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# HYPOTENSIVE ACTIONS OF SOME CHINESE MEDICINAL PLANTS
## - WITH EMPHASIS ON ACACIA CATECHU

BY

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## ABBREVIATIONS USED IN THIS THESIS

| | |
|---|---|
| MAP | Mean arterial pressure |
| AVP | Arginine vaspressin |
| ACE | *Acacia catechu* extract |
| COE | *Calendula officinalis* extract |
| CCE | *Clematis chinesis* extract |
| SFE | *Sargassum fusiforme* extract |

# ABSTRACT

There is a large number of medicinal plants which are reported to be hypotensive. However, due to the lack of systematic studies, their action mechanisms are mostly unknown. In the present study, the hypotensive effect of four Chinese medicinal plants were examined. They were *Calendula officinalis* L., *Acacia catechu* (L.) Willd, *Clematis chinensis* Osbeck and *Sargassum fusiforme* (Harv.) Setch. The water extracts of these four plants produced a dose-related decrease in MAP. The potencies and durations of response produced by these extracts were different. Except for *Calendula*, the hypotensive effect of these plant could not be ascribed to the magnesium, potassium and calcium ions present in the plant tissue.

The hypotensive action of *Acacia* extract (ACE) was further studied in more detail. It produced a dose-related decrease in the blood pressure of both anesthetized dogs and rats. In blocker studies, the hypotensive action of this plant extract was found not mediating via the following: the $\alpha$-adrenoceptor, $\beta$-adrenoceptor, muscarinic receptor, histamine-1, -2 receptor, the central nervous system. Captopril infusion potentiated the hypotensive responses by prolonging the duration of the response. It also relaxed

the isolated rat tail arteries in the AVP or methoxamine preconstricted condition. Furthermore, positive chronotropic and inotropic effects of ACE were demonstrated in the isolated rat atrium.

It is concluded that the hypotensive effect of ACE is ascribed to the presence of hypotensive peptide/s or protein/s, which produce vasodilatation.

# CHAPTER ONE

## GENERAL INTRODUCTION

Disease is an unseparable twin of life. In order to battle against this devil, human being acquires a wide spectrum of knowledge and develops a highly sophisticated system -- medical sciences. However, in the ancient world, before all the modern sciences blossomed, man could only get the helping hand from the Nature. Plants, due to their availability, diversity and their close relation with mankind, are inevitably noted and tried by man in therapeutic purposes.

The use of medicinal plants in the treatment of diseases in China is as ancient as the Chinese History. At first, the knowledge was perhaps passed on among generations and gradually these information were recorded. The first book of the Chinese medicinal plants to appear is the 'shennong pentcao' ( 神農本草 ) dated in the late Han Dynasty, about 100 A.D. After that, many books were available and nearly all of them bore the name 'pentcao' which means herbal. These literatures seemingly provide valuable information on ethnotherapeutics (1,2).

Although phytotherapy has been developed in China for such a long time, due to the lack of systematic studied and related knowledge from other branches of life sciences, the nature of the therapeutic properties of herbal medicines was completely unknown. Furthermore, the Chinese herbalists were so varied in their competences; their mystical explanations on diseases and drugs made people feel skeptical to this ancient "treasure".

On the contrary, western phytochemists began their studies of the chemical compositions of plant materials in the early nineteenth century. From that time onward, a large number of substances with high biological activities were isolated. These included cholinomimetic alkaloids, such as pilocarpine, muscarine and arecoline from *Pilocarpus* sp., *Amanita muscaria* and *Areca catechu* respectively; antimuscarinic alkaloids, e.g. atropine and scopolamine from *Atropa belladonna*; adrenergic neuron blocking alkaloid, e.g. from *Rauwolfia serpentina* Benth.; ganglionic stimulating alkaloids, nicotine and lobelia, from *Nicotiana tobacum* and *Lobelia inflata* respectively; neuromuscular blocking agents, curare, from *Chondrodendron* sp.; local anesthetics, cocaine, from *Erythroxylon coca*; opioid analgestics, morphine, from *Papaver somniferum*; central nervous stimulants, picrotoxin, theophylline, caffeine and theobromine, from *Anamirata cocculus* and *Thea sinensis*; aspirin-like drug, salicin and colchicine, and *Salix alba* and *Colchicum antumnale*; cardiac glycosides from Digitalis purpurea; anti-malaria drug, quinine, from cinchona plants; and antimetabolites, vinca alkaloids, from *Vinca rosea* Linn.(3).

Being stimulated by the western scientists, Chinese scientists, who are equipped with western techniques on one hand and the vast amount of informations accumulated for thousands of years on the other, began extensive researches on the phytochemistry and pharmacology of medicinal plants. In the past three decade, they isolated and synthesized many active compounds which can now shown to serve as antitumor, cardiovascular, contraceptive, anesthetics, sedative, CNS stimulatory, anti-bronchitis, anti-microbial, antiviral, anti-inflammatory, anti-hepatitis and anti-parasitic drugs (4,5).

It is beyond any doubt that the plant kingdom represents an inexhaustible source of new chemical compounds, many of them possess high biological activities. The late discovery of reserpine, such an efficient drug of plant origin against hypertension, was the turning point, in the view of most scientists, on the role of medicinal plants in contemporary medicine and the possibility of extracting rational grains from traditional medicine (7).

The present study examines the alleged hypotensive effect of some Chinese medicinal plants belonging to different families and I hope to contribute to a better understanding of the pharmacology of these plants, and of hypertension itself.

# CHAPTER TWO

# LITERATURE REVIEW

# SECTION ONE

# HYPOTENSIVE CHINESE HERBAL MEDICINE

Hypertension is the most widespread cardiovascular disease. Since it is very damaging and leads to severe diseases, such as angina pectoris, coronary occlusion, arteriosclerosis, cerebral hemorrhage (stroke) and renal disease, it becomes one of the focus of contemporary medicine. Thanks to the efficient drugs produced in the last two or three decades, doctors today can prevent the worsening of the disease upon diagnosis in many patients and save thousands of lives (8). However, healing or recovery of the patients (in essential hypertension) remains yet to be seen. Many patients have to be prescribed with drugs and/or dietary restraint till the end of their lives. This fact alone generates an ever growing interest in finding and producing more effective new drugs for the therapy of this disease.

## General Problems Associated with Chinese Medicinal Plants

Traditional informations on Chinese medicinal plants may give hints to the finding of new drugs. In fact, there are more than 200 species of plants in the Encyclopedia of Chinese Drugs which are reported to be hypotensive and/or antihypertensive. However, when we speak about the possible application of traditional medicine, we should identify the positive principles in them. One of the greatest difficulties in decoding traditional medicine's indications is insufficient specificity. For instance, some herbs are recommended for the treatment of

" womwn's diseases" which includes dozens of different diseases requiring different treatments. Indeed it represents a whole branch of medicine, i.e. gynecology. It is often said that this or that herb is helpful in the treatment of hydropsy, i.e. oedema and ascites. However, the causes of development of oedema and ascites might be the result of heart, kidney, liver, endocrine, metabolic or other disease (7). It is essential to verify the data in the traditional medicine by using various experimental models and based on these scientific data, classify the plants according to their ability to ameliorate various types of diseases.

Another difficulty is the identification of the medicinal plants. It is not unusual to note that the common name of a Chinese medicinal herb may represent plants of different genera or even different families. For instances, jin quian cao (金錢草 ) may be knoen to represent *Glechoma longituba* (Kakai) Kupr, *Lysimachia christinae* Hance, *Dichondra repens* Forst, *Hydrocotyle sibthorpioides* Lam. var. batrachium (Hance) Handi.-Mazz. or *Desmodium styracifolium* (Osbeck) Merr. but in fact these belong to family Labiatae, Primulales, Convolvulaceae, Umbelliferae and Lequminosae respectively (9). This may be due to the fact that the herbal collectors do not have a good training in identifying the medicinal plants or, more probably, they are taught with different school of taxononmy. Howver, it is interesting that these five different plants all share two common therapeutic properties: anti-fever and diuretic (10). This suggests that some plants with similar properties are used as substitutes in some places where the original plant species is unavailable. So, for the elucidation of the medicinal properties of a particular plant, knowledge of its botanical and pharmacognostical aspects is necessary. Of the common Chinese medicinal plants being sold in drug stores these have been dried for the convenience of storage, transfer etc. This makes either the pharmacognostical or botanical studies difficult. In the final analysis, the various chemical constituents (chemotaxonomy) in these medicinal materials are of prime importance. But, unfortunately, information on this aspect is scarce in most cases.

Special attentions have to be paid to the different parts of the medical plants, only certain parts of the plants possess the therapeutic properties. Furthermore, different floral parts may have quite different pharmacological actions, e.g. the fruit of Ligustrum lucidum Ait. is cardiotonic and diuretic, while its leaves have anti-microbial actions (11).

The traditional regimens of Chinese medicine rarely consist of a single drug, they are in the form of combinations. The combinations basically follow three principles: 1) Effectiveness can be increased by using combination of drugs of similar properties, e.g. the inflorescence of Chrysanthemum indicum L. together with the whole plants of Taraxacum mongolicum Hand.-Mazz.: their anti-fever action will be increased. 2) Effectiveness can be increased by the interaction of drugs of different properties. For example, the root of Astragalus baicalensis together with root nodules of Poria coca (Schw.) Wolf. can promote the actions of invigorate the spleen, promote vital energy and diuresis. 3) The addition of a drug to antagonize the toxic or side effect of the other can promote the therapeutic value of the other drugs. For instance, the root of Zingiber officinale Rosc. can deprive the toxic effect of Pinellia ternata (Thunb.) Breit. and synchronize its anti-vomiting and phlegm-controlling actions (12). These combinations show further complications for unravelling the already masked properties of Chinese medicinal plants.

## Selection of Research Materials : Some Guiding Principles

The plants reportedly effective in producing hypotension are listed in Table 2.1.1, herein after they are referred as hypotensive plants. Ther are 345 species and 234 genera belonging to 94 different families, among Phaeophyta, Eumycetes, Lichens, Bryophyta, Gymnospermae and Anfiospermae. Most of these hypotensive plants are angiosperms, and the ten largest families of these hypotensive plants are: Compositae, Apocynaceae, Leguminosae, Rubiaceae, Ranunclaceae, Liliaceae, Menispermaceae, Umbelliferae and Berberidaceae (Table 2.1.2). All except Lilaceae (monocot) are families of dicotyledonous plants.

Plants that are closely related phylogenetically usually have similar chemical componds. Gottlieb (13) studied the occurrence of biological active chemicals in Brazilian angiosperms. He showed that the specific biologically active compounds are quite systematically located in the plant kingdom and thus it is possible to predict the existence of these useful chemicals in the related plant taxa. With this idea, I have assigned the hypotensive plants into Dahlgnen's system (14) of classification to see any coincidence of their distribution with the evolutionary rationale. It is reasonable to surmise that the hypotensive and other therapeutic properties of Chinese herbal medicines are ascribed to the presence of active chemical components in the plant material, despite many groups of chemicals are involved (see next section).

The analysis of Fig. 2.1.1 shows that Ranunculiflorae (57 species) Cronquist's (15) subclass of Magnoliidae , and Asteriflorae (39 species) and Gentianiflorae (41 species) Cronquist's subclass of Asteridae are the most popular superorder of the hypotensive plants (Table 2.1.3). This agrees with Gottlieb's finding that most of the biologically active compounds are produced by the primitive Magnoliidae or the advanced Asteridae (13). However, the present finding also shows a wide distribution of hypotensive plants in Rosidae (27 species in Rosiflorae and 17 species in Rutiflorae), which seems to have relatively few useful compounds in their Brazilian counterpart.

In the study of the Chinese medicinal plants, I think it would be quite unprudent if one neglect their " traditional" classifications. One of the "traditional" system separates the plants according to their flavors and their natures. There are basically five different flavors: acrid, sweet, bitter, sour and salty. It might seem superficial to classify a drug according to its flavor, however, in Chinese medicine each of these five flavors represents a distinct group of pharmacological properties. Acrid plants can induce sweating, promote "vital energy circulation" and alleviate pain. Sour plants can stop sweating and have astringent property. Sweet plants can "invigorate vital energy" and "enrich the blood". Bitter-flavored plants have the properties of "purging fire", depriving the "evil wetness" and stoping diarrhea. Salty-flavored plants plants have the effects of softening the dry faeces and "relaxing the bowls". There are some plants with no distinct flavor which are known as the bland flavored plants, and which usually possess diuretic and edema-relieving properties (12,16).

With reference to their flavors, the hypotensive plants are divided and listed in Table 2.1.4. Since some plants possess more than one flavor, so a single plant may appear in more than one category. The most popular flavor is bitter, which includes 42.77% (189 species) of the hypotensive plant population. The sweet and acrid flavors are the second and the third popular groups which represents 25.67% (113 species) and 22.62% (100 species) respectively.

The Chinese medicinal plants can also be divided into four natures: cold, hot, cool and warm. The nature of a plant is mainly determined by its therapeutic effects. Generally speaking, plants with cold and cool natures are used for anti-fever, purging fire and detoxication, while plants with hot and warm natures are employed for expelling cold, warming the interior and restoring Yang ( 陽 ). Besides these four natures, there are some plants which have the properties in between cool and warm, and are known as mild-natured plants (12,16).

In Table 2.1.5, the hypotensive plants are classified according to their natures. Although not all natures of the listed plants are known, they still reflect their distribution in the traditional system. 34.33% (103 species) of the hypotensive plants are cool in nature and 16% (48 species) are the cool nature plants. They constitute about half of the hypotensive plant population. The another half consists of warm-nature and mild-nature plants, which represent 26% (78 species) and 22.67% (68 species) respectively. There is only one percent (3 species) of plants belonging to the hot-nature plants. It should be noticed that the cold-nature plants are usually with bitter flavor and they both share the property of purging fire. The plants which are bitter with cold nature, solely occupy 19.10% of the hypotensive plants. A previous study conducted by chinese investigators found that 77.3% of the 136 kinds of hypotensive medicinal drugs of either plant and animal origin belonged to the cool and cold-nature drugs, while 11.4%of them belonged to the warm-nature drugs. This coincides with the traditional clinical experiences, that hypertension is a warm disease and is therefore treated with cold and cool-nature drugs.

It is now beyond any doubt that the plant kingdom can function as a great and valuable source for exploring potent hypotensive drugs, leading to the ultimate cure of hypertension. I hope the information from traditional Chinese medicine can give some clues for this great search.

Table 2.1.1 Plants with Hypotensive Actions

| | | | |
|---|---|---|---|
| Laminariaceae | | | |
| Ecklonia kurome Okan. | leaves * | salty with cold nature ** | |
| Laminaria japonica Aresch. | | | |
| Undaria pinnatifida (Harv.) Sur. | | | |
| Sargassaceae | | | |
| Sargassium fusiforme (Harv.) Setch. | whole plant | bitter and salty with cold nature | |
| Sargassium pallidium (Turn) C. Ag. | | | |
| Polyporaceae | | | |
| Ganoderma lucidum (Leyss. ex Fr.) Karst. | whole plant | sweet with mild nature | (18) |
| Ganoderma japonicum (Fr.) Lloyd. | | | |
| Cladoniaceae | | | |
| Cladonia alpestris (L.) Rabht. | lichen mass | bland with mild nature | |
| Stereocaulon paschale Hoffm. | lichen mass | bitter with cold nature | |
| Usneaceae | | | |
| Usnea longissima Ach. | rhizome | bitter and sweet with mild nature | |
| Usnea diffracta Vain. | | | |
| Dermatocapon miniatum (L.) Mann. | lichen mass | bitter and bland with mild nature | (19) |
| Equisetaceae | | | |
| Equisetalum arvense L. | whole plant | bitter with cold nature | |
| Aspidiaceae | | | |
| Cyrtomium fortunei J. Sm. | root | bitter with cold nature | |
| Dryopteris laeta (Kom.) C. Chr. | root | bitter with mild nature | |
| Cycadaceae | | | |
| Cycas revoluta Thunb. | seed | sweet with mild nature | (20) |
| Pinaceae | | | |
| Abies sutchuerensis (Franch.) Rehd. et. Wils. | fruit | acrid with mild nature | |
| Cupressaceae | | | |
| Biota orientalis (L.) Endl. | young shoot and leaves | bitter with cold nature | |

* Active part of the plant ** Properties of the plant

| | | | |
|---|---|---|---|
| Piperaceae | | | |
| *Piper longum* L. | root | acrid with warm nature | |
| Salicaceae | | | |
| *Salix babylonica* L. | leaf | bitter with cold nature | |
| Juglandaceae | | | |
| *Juglans regia* L. | leaf | sweet with warm nature | |
| Fagaceae | | | |
| *Lithocarpus polystachyus* Rehd. | leaf | sweet | |
| Casuarinaceae | | | |
| *Ephedra sinica* Stapf. | root | sweet with mild nature | (6) |
| Eucommiaceae | | | |
| *Eucommia ulmoides* Oliv. | bark | bitter and sweet with warm nature | (21,22) |
| Moraceae | | | |
| *Ficus carica* L. | receptacle | sweet with mild nature | |
| *Cannabis sativa* L. | seed | sweet with mild nature | |
| *Morus alba* L. | young shoot,<br>root and root bark | bitter with mild nature<br>sweet with cold nature | (6) |
| Urticaceae | | | |
| *Urtica angustifola* Fisch. ex. Hornem. | root | bitter and acrid | |
| *Urtica cannabina* L. | | | |
| Loranthaceae | | | |
| *Viscum album* L. | stem and leaf | sweet and bitter with mild nature | (7,23) |
| *Viscum articulatum* Burm. f. | stem | acrid with mild nature | |
| *Viscum coloratum* (Kom.) Nakai | shoot leaf | bitter and sweet with mild nature | |
| *Loranthus parasiticus* (L.) Merr. | | | |
| *Loranthus yadoriki* Sieb. | | | |
| *Gardenia jasminoides* Ellis | fruit | bitter with cold nature | |
| Aristolochiaceae | | | |
| *Aristolochia contorta* Bge. | fruit or root | bitter with cold nature | |
| *Aristolochia debilis* Sieb. et. Zuce. | | | |
| *Asarum heterotropoides* F. Schm. var. mandshuricum (Maxim.) Kitag. | whole plant | acrid with warm nature | |
| *Asarum sieboldii* Miq. | | | |

| | | | |
|---|---|---|---|
| Polygonaceae | | | |
| *Fagopyrum esculentum* Moench | leaf | sour with cold nature | |
| *Polygonum aviculare* L. | whole plant | bitter with cold nature | |
| *Polygonum chinense* L. | whole plant | sour and sweet with cool nature | |
| *Polygonum hydropiper* L. | whole plant | acrid with mild nature | |
| Chenopodiaceae | | | |
| *Salsola ruthenica* Iljin. | whole plant | bitter with cool nature | |
| *Salsola collina* Pall. | whole plant | bland with cool nature | |
| Amaranthaceae | | | |
| *Achyranthes bidentata* Bl. | root | bitter, sweet and sour | |
| *Achyranthes aspera* L. | whole plant | bitter and acrid with cold nature | (24) |
| *Celosia argentae* L. | fruit | bitter with cool nature | |
| Caryophyllaceae | | | |
| *Stellaria saxatilis* Buch.-Ham. | whole plant | hot | |
| *Cerastium viscosum* L. | whole plant | sweet | |
| *Malachium aquaticum* (L.) Fries. | whole plant | sweet and bland with mild nature | |
| Euphorbiaceae | | | |
| *Phyllanthus emblica* L. | root | sweet with cold nature | (20) |
| Magnoliaceae | | | |
| *Magnolia liliflora* Desr. | bark | bitter with cold nature | |
| | flower bud | acrid with warm nature | |
| *Magnolia denudata* Desr. | flower bud | acrid with warm nature | |
| *Talauma mexicana* | flower and seed | --- | (23) |
| Lauraceae | | | |
| *Cinnamonum cassia* Presl. | bark | bitter and sweet with hot nature | |
| *Lindera umbellata* Ramus | root bark | warm nature | (25) |
| Ranunculaceae | | | |
| *Aconitum carmichaeli* Debx. | root | acrid with hot nature | |
| *Aconitum kusnezoffii* Rehb. | | | |
| *Cimicifuga acerina* (Sieb. et. Zucc.) Tanaka | root | bitter and sweet with cold nature | |
| *Cimicifuga dahurica* (Turcz.) Maxim. | stem | acrid, sweet and bitter with cold nature | |

| | | |
|---|---|---|
| *Cimicifuga foetida* L. | | |
| *Cimicifuga heracleifolia* Kom. | | |
| *Cimicifuga simplex* Wormsk. | root | acrid, sweet and bitter with cold nature |
| *Clematis chinensis* Osbeck | root | acrid and salty with warm nature |
| *Coptis chinensis* | root | bitter with cold nature |
| *Coptis deltoidea* C.Y. Cheng et. Hsiao | | |
| *Coptis omeiensis* (Chen) C.Y. Cheng | | |
| *Coptis teetoides* C.Y. Cheng | | |
| *Paeonia lactiflora* Pall. | root | sour, bitter with cold nature |
| *Paeonia obovata* Maxim. | | |
| *Paeonia suffruticosa* Andr. | root bark | acrid and bitter with cool nature |
| *Paeonia veitchii* Lynch | root | sour and bitter with cold nature |
| *Ranumculus chinensis* Bge | whole plant | bitter with warm nature |
| *Solanum nigrum* L. var. paueiflorum | whole plant | bitter with cold nature |
| *Thalictrum foliolosum* | root | bitter with cold nature |
| *Thalictrum baicalense* Turcz. | | |
| *Thalictrum rhynchocarpum* Dill & Rich. | root | |
| Berberidaceae | | |
| *Berberis amurensis* Rupr. | root, shoot | bitter with cold nature |
| *Berberis poiretii* Schneid | | |
| *Berberis thunbergii* D.C. | | |
| *Berberis sargentiana* Schneid | | |
| *Berberis brachypoda* Maxim. | | |
| *Berberis dictyophylla* Franch var. epruinosa Schneid | root bark | bitter with cold nature |
| *Berberis heteropoda* Schrank | bark | bitter with cold nature |
| *Epimedium grandiflorum* Morr. | stem and leaf | acrid and sweet with warm nature |
| *Epimedium brevicornum* Maxim | | |
| *Epimedium sagittatum* (Sieb. et. Zucc.) Maxim. | | |
| *Leontice robustum* (Maxim.) Diels | root | acrid with warm nature |

| | | | |
|---|---|---|---|
| *Mahonia bealei* (Fort.) Carr. | leaf | bitter with cold nature | |
| *Mahonia fortunei* (Lindl.) Fedde | | | |
| *Mahonia japonica* (Thunb) D.C. | | | |
| Menispermaceae | | | |
| *Aristolochia fangchi* Wu. | root | bitter with cold nature | |
| *Aristolochia heterophylla* Hemsl | | | |
| *Cocculus laurifolius* D.C. | whole plant | --- | |
| *Cocculus trilobus* (Thunb.) D.C. | root | bitter with cold nature | |
| *Diploclisia chinensis* Merr. | shoot | bitter with mild nature | |
| *Menispermum dauricum* D.C. | stem | --- | (26,27) |
| *Sabia japonica* Maxim. | shoot | bitter with mild nature | |
| *Sinomenium acutum* (Thunb.) Rehd. | | | |
| *Stephania cepharantha* Hayata | root | acrid and bitter with cold nature | |
| *Stephania delavayi* Diels. | | bitter and acrid with cold nature | (7) |
| *Stephania japonica* (Thunb.) Miers | whole plant | bitter with cold nature | |
| *Stephania tetrandra* S. Moore | root | bitter with cold nature | |
| Nymphaeaceae | | | |
| *Nelumbo nucifera* Gaertn. | embryo | bitter with cold nature | |
| *Nymphaea tetragona* Georgi | flower | --- | |
| Papaveraceae | | | |
| *Chelidonium majus* L. | whole plant with flower | bitter and acrid with warm nature | |
| *Corydalis decumbens* (Thunb.) Pers. | whole plant | | |
| *Dactylicapnos scandens* | root | | |
| Cruciferae | | | |
| *Capsella bursa* (L.) Medic | whole plant | sweet with mild nature | (20) |
| *Erysimum cheiranthoides* L. | whole plant | sour and bitter with mild nature | |
| *Erysimum aurantiacum* (Bge.) Maxim. | | | |
| Crassulaceae | | | |
| *Sedum multicaule* Wall. | stem and leaf | acrid and sweet with cold nature | |
| *Sedum kamtschaticum* Fisch. | whole plant | sour with mild nature | |

| | | | |
|---|---|---|---|
| Pittosporaceae | | | |
| *Pittosporum blabratum* Lindl. | root | bitter and acrid with warm nature | |
| Rosaceae | | | |
| *Crataegus pinnatifida* Bge. var. major N.E. Br. | fruit or leaf | sour and sweet with warm nature | |
| *Crataegus cunneata* Sieb. et. Zuce. | | | |
| *Crataegus oxyacantha* | leaf and blossom | sweet with cool nature | (7) |
| *Crataegus monogina* | | | |
| *Malus pumila* Mill. | fruit | sweet with cool nature | |
| Leguminosae | | | |
| *Acacia catechu* (L.) Willd. | shoot and leaf | bitter with cold nature | |
| *Arachis hypogaea* L. | stem and leaf | --- | |
| *Astragalus chrysopterus* Bge. | root | sweet with warm nature | |
| *Astragalus dasyanthus* Pall. | | | (7) |
| *Astragalus floridus* Benth. | | | |
| *Astragalus membranaceus* (Fisch.) Bge. | | | |
| *Astragalus mongholicus* Bye. | | | |
| *Astragalus tongolensis* Ulbr. | | | |
| *Caesalpinia crista* L. | leaf | bitter with cool nature | |
| *Caragana sinica* (Buc'hoz) Rehd. | root | acrid and bitter with mild nature | |
| *Cassia occidentalis* L. | fruits and seed | bitter with cool nature | |
| *Cassia tora* L. | seed | bitter and sweet with cool nature | (20) |
| *Piptanthus concolor* Harrow | seed | sweet and bland with cold nature | |
| *Pueraria lobata* | root | sweet with mild nature | (4) |
| *Sophora japonica* L. | flower | bitter with cool nature | |
| *Thermopsis alpina* Ledeb. | root | bitter with cold nature | |
| *Vicia faba* L. | flower | sweet with mild nature | |
| Sterculiaceae | | | |
| *Helicteres angustifolia* L. | whole plant | bitter with cool nature | |
| *Sterculia scaphigera* Wall. | seed | sweet and bland with cool nature | |
| Malvaceae | | | |
| *Hibiscus rosa-sinens* | flower | sweet with cold nature | |

| | | | |
|---|---|---|---|
| Geraniaceae | | | |
| *Geranium macrorrhizum* L. | rhizome | bitter with mild nature | (7) |
| Zygophyllaceae | | | |
| *Nitraria sibirica* | fruit | sweet, sour and salty with warm nature | |
| *Peganum harmala* L. | seed | bitter with warm nature | |
| *Tribulus terrestris* L. | fruit | bitter and acrid with warm nature | |
| Rutaceae | | | |
| *Casimiroa edulis* | seed | --- | (23) |
| *Citrus erythrosa* Tanaka | fruit coat | acrid and bitter with warm nature | |
| *Citrus tangerina* Hort. et. Tanaka | | | |
| *Evodiae fruitus* | fruit | | |
| *Evodia rutaecarpa* (Juss.) Benth. | fruit | acrid and bitter with warm nature | |
| *Phellodendron amurense* Rupr. | bark | bitter with cold nature | |
| *Phellodendron chinense* Schneid | | | |
| *Toddalia asiatica* (L.) Lam | root | acrid and bitter with warm nature | (6) |
| *Zanthoxylum bungeanum* | fruit coat | acrid with warm nature | |
| Burseraceae | | | |
| *Olea europea* | leaf | --- | (7) |
| Anacardiaceae | | | |
| *Anacardium occidentale* L. | fruit | sweet with mild nature | (24) |
| Sapindaceae | | | |
| *Cardiospermum halicacabum* L. | whole plant | bitter with cold nature | |
| *Sapindus mukorossi* Gaertn. | fruit | bitter with mild nature | |
| *Sapindus trifoliatus* L. | | | |
| Celastraceae | | | |
| *Celastrus orbiculatus* Thunb. | stem | acrid with warm nature | |
| Aquifoliaceae | | | |
| *Ilex pubescens* Hook. et Arn. | root | sweet and bitter with mild nature | (4) |
| Rhamnaceae | | | |
| *Ziziphus jujuba* Mill. var. inermis | fruit | acrid with warm nature | |
| (Bge.) Rehd. | seed | sweet with mild nature | |
| | root bark | astrigent with warm nature | |

| | | | |
|---|---|---|---|
| Caricaceae | | | |
| *Carica papaya* L. | young leaf | --- | (24) |
| Passifloraceae | | | |
| *Adenia cissampeloides* (Planch. ex Benth.) Harms | --- | | |
| Cactaceae | | | |
| *Echinocereus triglochidiatus* Engelm. var. neomexicanus (Standley) Standley ex W.T. Marshall | whole plant | | (31) |
| Combretaceae | | | |
| *Terminalia arjuna* | bark | | (28) |
| Araliaceae | | | |
| *Aralia elata* (Mig.) Seem. | bark | acrid with mild nature | |
| *Panax ginseng* C.A. Mey | root | bitter and sweet with warm nature | |
| *Panax pseudo-ginseng* Wall. var. notoginseng (Burkill) Hoo & Tseng | root<br>flower | bitter and sweet with warm nature<br>sweet with cool nature | (29,30) |
| Umbelliferae | | | |
| *Anethum graveolens* L. | leaf | acrid with warm nature | |
| *Angelica sinensis* (Oliv.) Diels. | root | acrid with warm nature | (32,33,34) |
| *Apium graveolens* L. var. dulce D.C. | whole plant | sweet and bitter with cool nature | |
| *Oenanthe benghalensis* (Roxb.) Kurz. | whole plant | acrid with cool nature | |
| *Oenanthe javanica* (Bl.) D.C. | whole plant | sweet with cold nature | |
| *Ligusticum wallichii* Franch. | root and shoot | acrid with warm nature | |
| *Peucedanum arenarium* | root | bitter and acrid with cool nature | (7) |
| Pyrolaceae | | | |
| *Pyrola rotundifolia* L. | whole plant | bitter and sweet with warm nature | |
| Ericaceae | | | |
| *Andromeda polyfolia* | leaf | --- | (7) |
| *Rhododendron micranthum* Turcz. | stem, leaf and flower | acrid with warm nature | |
| *Rhododendron molle* (Bl.) G. Don. | fruit<br>inflorescence | bitter with warm nature<br>acrid with warm nature | |

| | | | |
|---|---|---|---|
| Myrsinaceae | | | |
| <u>Ardisia</u> <u>japonica</u> (Horrs.) Bl. | stem and leaf | bitter with mild nature | |
| <u>Lysimachia</u> <u>vulgaris</u> L. var. davurica (Ledeb.) R. Knuth. | whole plant | --- | |
| <u>Maesa</u> <u>indica</u> Wall. | whole plant | bitter with cool nature | |
| Primulaceae | | | |
| <u>Lysimachia</u> <u>barystachys</u> Bye. | whole plant | bitter and sour with mild nature | |
| <u>Lysimachia</u> <u>hattiana</u> Hance | whole plant | --- | |
| <u>Lysimachia</u> <u>insignis</u> Hemsl. | whole plant | bitter and acrid with warm nature | |
| Plumbaginaceae | | | |
| <u>Plumbago</u> <u>indica</u> L. | stem, leaf and flower | acrid with warm nature | |
| Ebenaceae | | | |
| <u>Diospyros</u> <u>kaki</u> | fruit | bitter | (6) |
| Symplocaceae | | | |
| <u>Symplocos</u> <u>caudata</u> Wall. | leaf | sour and sweet | |
| Oleaceae | | | |
| <u>Ligustrum</u> <u>japonicum</u> Thunb. var. pubescans Koidz. | leaf | bitter and sweet with cool nature | |
| Loganiaceae | | | |
| <u>Mostuea</u> <u>hirsuta</u> (Anders ex Benth) Baill. ex Bak. | root | | (24) |
| Gentianaceae | | | |
| <u>Swertia</u> <u>heterantha</u> Ling. | whole plant | sweet and bitter with mild nature | |
| <u>Gentiana</u> <u>crassicaulis</u> Duthie ex. Burkill | root | acrid and bitter with mild nature | |
| <u>Gentiana</u> <u>macrophylla</u> | | | |
| <u>Gentiana</u> <u>scabra</u> Bge. | root | bitter with cold nature | |
| <u>Gentiana</u> <u>tibetica</u> King | root | acrid and bitter with mild nature | |
| <u>Gentiana</u> <u>triflora</u> Pall. | root | bitter with cold nature | |
| Apocynaceae | | | |
| <u>Alstonia</u> <u>yunnanensis</u> Diels. | root | --- | |
| <u>Apocynum</u> <u>venetum</u> L. | whole plant | sweet and bitter with cool nature | |

| | | | |
|---|---|---|---|
| *Catharanthus lanceus* | leaf and roots | --- | (35) |
| *Catharanthus roseus* (L.) G. Don. | whole plant | bitter with cool nature | |
| *Chonemorpha megacalyx* Pier. | stem | acrid with warm nature | |
| *Ervatamia hainaensis* Tsiang | root | bitter and acrid with warm nature | |
| *Hunteria eburnea* Pichon | seeds, stembark and rootbark | --- | (24) |
| *Holarrhena antidysenterica* Wall. | bark | --- | |
| *Vinca minor* L. | | --- | (20) |
| *Rauwolfia serpentina* Benth. ex. Kurz. | root | bitter with cold nature | (36,7) |
| *Rauwolfia tetraphylla* L. | root | | (36) |
| *Rauwolfia verticillata* (Lour.) Baill. | root | | |
| *Rauwolfia vomitoria* Afzel. | root | | (24,36) |
| *Picralina nitida* Stapf. | seed | --- | (24) |
| *Tabernaemontana pachysiphon* Stapf. | root | --- | (24) |
| *Voacanga africana* Stapf. | stembark and rootbark | --- | (24) |
| *Holarrhena floribunda* (Don) Dur. & Schinz var. floribunda | stembark and rootbark | --- | (24) |
| Asclepiadaceae | | | |
| *Cynanchum paniculatum* (Bge.) | root and stem | acrid with warm nature | |
| *Cryptolepis sanguinolenta* (Lindl.) Schltr. | root | | (24) |
| Convolvulaceae | | | |
| *Convolvulus arvensis* L. | whole plant and flower | salty with warm nature | |
| *Ipomoea digitala* L. | root and leaf | bitter with cold nature | |
| Boraginaceae | | | |
| *Cynoglossum officinale* L. | root | sweet with mild nature | |
| *Heliopium indicum* L. | root or whole plant | bitter with mild nature | |
| Verbenaceae | | | |
| *Clerodendron bungei* Steud. | root | acrid and bitter with warm nature | |
| | stem and leaf | acrid and bitter | |
| *Clerodendron fragrans* Vent. | root and leaf | bland with mild nature | |
| *Clerodendron trichotomium* Thunb. | young shoot and leaf | bitter and sweet | |
| | root | bitter with cold nature | |

| | | | |
|---|---|---|---|
| *Clerodendron yunnanense* Hu ex Hand.-Mazz. | whole plant | acrid and bitter with warm nature | |
| *Heliotropium indicum* L. | seeds, whole plant and root | bitter with mild nature | (37) |
| *Lantana camara* L. | root | sweet and bitter with cold nature | |
| | young shoot | bitter with cold nature | |
| Labiatae | | | |
| *Ajuga lupulina* Maxim. | whole plant | bitter with cold nature | |
| *Anisomeles indica* (L.) O. Ktze. | whole plant | acrid and bitter with warm nature | |
| *Dracocephalum heterophyllum* | whole plant | acrid and bitter with cold nature | |
| *Glechoma longituba* (Nakai) Kupr. | whole plant | acrid and bitter with cool nature | |
| *Leonurus heterophyllus* Sweet | whole plant | acrid and bitter with cool nature | |
| *Mesona chinensis* Benth. | whole plant | sweet and astringent with cold nature | (19) |
| *Prunella vulgaris* L. | fruit and inflorensence | sweet and bitter with cold nature | |
| *Rosmarinus officinalis* L. | whole plant | acrid with warm nature | |
| *Salvia miltiorrhiza* Bge. | root | bitter with warm nature | |
| *Scutellaris baicalensis* Georgi | root | bitter with cold nature | |
| Solanaceae | | | |
| *Lycium chinense* Mill. | root bark | sweet with cold nature | (22) |
| *Scopolia acutangula* C.Y. Wu et. C.Chen | leaf, root and seed | bitter with warm nature | |
| Scrophulariaceae | | | |
| *Linaria vulgaris* Mill. | whole plant | bitter and sweet with cold nature | |
| *Rehmannia glutinosa* (gaertn.) Libosch. | root and shoot | sweet and bitter with cool nature | |
| *Rehmannia glutinosa* Libosch. F. hueichingensis (Chao et Schih) Hsiao. | | | |
| *Scrophularia ningpoensis* Hemsl. | root | salty and bitter with cool nature | |
| *Verbascum thapsus* L. | whole plant | acrid and bitter with cold nature | |
| *Veronica anagallis-aquatica* L. | whole plant | bitter with cool nature | |

| | | | |
|---|---|---|---|
| Orobanchaceae | | | |
| *Cistanche ambigua* (Bge.) G. Beck. | shoot | sweet, sour and salty with warm nature | |
| *Cistanche deserticola* Y.C. Ma | | | |
| *Cistanche salsa* (C.A. Mey.) G. Beck. | | | |
| Bignoniaceae | | | |
| *Tecomaria capensis* (Thunb.) Spach. | root or leaf | acrid and bitter with cool nature | |
| Acanthaceae | | | |
| *Andrographis panicolata* (Burm. f.) Nees. | whole plant | bitter with cold nature | |
| Plantaginaceae | | | |
| *Plantage asiatica* L. | whole plant or seed | sweet with cold nature | |
| *Plantago depressa* Willd. | | | |
| Rubiaceae | | | |
| *Corynanthe pachyceras* Schum. | bark | | (24) |
| *Galium aperine* L. | whole shoot | acrid and bitter with cold nature | |
| *Galium asperifolium* Wall. | | | |
| *Ixora chinensis* Lam. | flower | acrid with cold nature | |
| *Mitragyna inermis* (Willd.) Ktze. | bark and leaf | | (24) |
| *Mitragyna stipulosa* (D.C.) Ktze. | | | |
| *Paederia scandens* (Lour.) Merr. | whole shoot and root | sweet and sour with mild nature | |
| *Pausinystalia johimbe* (Schum.) Pierre Pierre ex Beille | bark | | (24) |
| *Serissa serissoides* (D.C.) Druce | whole plant | acrid with cool nature | (38) |
| *Uncaria macrophylla* Wall. | shoot | sweet and bitter with cool nature | |
| *Uncaria rhynchophylla* (Miq.) Jacks | stem | sweet with cool nature | (4) |
| *Uncaria sinensis* (Oliv.) Havil. | | | |
| *Morinda lucuda* Benth. | stem, bark, root and leaves | | (24) |
| Valerianaceae | | | |
| *Valeriana officinalis* L. | root | acrid and bitter with warm nature | (7,39) |

| | | | |
|---|---|---|---|
| Campanulaceae | | | |
| *Codonopsis lanceolata* Benth. et Hook. | root | sweet and acrid with mild nature | |
| *Codonopsis pilosula* (Franch.) Nannf. | root | sweet with mild nature | |
| *Lebelia chinensis* Lour. | whole plant | sweet with mild nature | |
| Compositae | | | |
| *Achillea millefolium* L. | whole plant | sweet, acrid and bitter with cold nature | |
| *Anaphalis nepalensis* (Spr.) Hand.-Mazz. | whole plant | sweet with mild nature | |
| *Artemisia capillaris* Thunb. | leaf | acrid and bitter with cool nature | (20) |
| *Bidens tripartita* L. | whole shoot | sweet and bitter with mild nature | |
| *Blumea balsamifera* D.C. | leaf and young shoot | acrid and bitter with warm nature | |
| *Blumea densiflora* (Heyne) D.C. | whole plant | bitter with cold nature | |
| *Calendula arvensis* L. | whole plant and flower | | |
| *Calendula officinalis* L. | flower and root | bland with mild nature | |
| *Capesium abrotanoides* L. | root and leaf | acrid with cold nature | |
| *Carduus crispus* L. | whole plant and root | bitter with mild nature | |
| *Carduus acanthoides* L. | | | |
| *Carthamus tinctorius* L. | flower | acrid with warm nature | (40) |
| *Cephalanoplos segetum* (Bge.) Kitam. | whole plant or root | sweet with cool nature | |
| *Chrysanthemum indicum* L. | flower | acrid and bitter with cool nature | (20) |
| *Chryvanthemum boreals* Mark. | | | |
| *Chrysanthemum lavandulaefolium* (Fisch.) Mak. | . | | |
| *Chrysanthemum morifolium* Ramat. | flower | sweet and bitter with cool nature | |
| *Cirsium japonicum* D.C. | root or whole plant | sweet with cool nature | (38) |
| *Echinops latifolius* Tausch. | stem | bitter and salty with cold nature | |
| *Eupatorium lindleyanum* D.C. var. trifoliolatum Mak. | whole plant | bitter with mild nature | |
| *Gnaphalium uliginosum* L. | whole plant | sweet and mild nature | |

| | | | |
|---|---|---|---|
| *Gnaphalium hypoleueum* D.C. | whole plant | sweet and bitter with mild nature | |
| *Helianthus annuus* L. | flower | sweet with warm nature | |
| | leaf | | |
| | receptacle | | |
| | whole plant | | |
| *Ixeris chinensis* (Thunb.) Makai | whole plant | | |
| *Rhaponticum uniflorum* | stem | bitter and salty with cold nature | |
| *Saussurea lappa* Clarke | root | acrid and bitter with warm nature | |
| *Siegesbeckia orientalis* L. | whole plant | bitter with cold nature | (20) |
| *Siegesbeckia orientalis* L. var. pubesceus Mak. | | | |
| *Siegesbeckia orientalis* L. var. glabrescens Mak. | | | |
| *Wedelia chinensis* (Osb.) Merr. | whole plant | sour and sweet with cool nature | (20) |
| *Wedelia prostrata* (Hook. et. Arn.) Hemsl. | whole plant | sour and sweet with mild nature | |
| *Vernonia colorata* (Willd.) Drake. | leaf | --- | (24) |
| *Vladimiria denticulata* Ling. | root | acrid and bitter with warm nature | (24) |
| *Vladimiria souliei* (Franch.) Ling. | | | |
| *Xanthium sibiricum* Patr. ex. Widd. | root | warm nature | |
| Typhaceae | | | |
| *Typha angustata* Bory et. Chaub. | pollen | acrid and sweet with cool nature | |
| *Typha angustifolia* L. | | | |
| *Typha latifolia* L. | | | |
| Alismaceae | | | |
| *Alisma plantago-aquatica* L. var. orientale Samuels | shoot | sweet with cold nature | |
| Gramineae | | | |
| *Arundo donax* L. | root | bitter with cold nature | |
| *Imperata cylindrica* (L.) P. Beauv. var. major (Nees) C.E. Hubb. | root | sweet with cold nature | (38) |
| *Panium repens* L. | root | sweet and bitter with mild nature | |
| *Zea Mays* L. | style | sweet with mild nature | (38) |

| | | | |
|---|---|---|---|
| Palmae | | | |
| *Trachycarpus wagnerianus* Becc. | fruit | bitter with mild nature | |
| | leaf | --- | |
| | plumal tissue | bitter with mild nature | |
| | bark | | |
| | flower | | |
| Araceae | | | |
| *Acorus calamus* L. | root | acrid and bitter with warm nature | |
| Commelinaceae | | | |
| *Commelina communia* L. | whole plant | bitter with cold nature | |
| Liliaceae | | | |
| *Allium sativum* | shoot | acrid with warm nature | (24) |
| *Allium ursinum* | shoot and stem | acrid with warm nature | (7) |
| *Asparagus officinalis* L. | root | sweet and bitter with warm nature | |
| *Fritillaria cirrhosa* D.Don. | shoot | bitter and sweet with cool nature | |
| *Fritillaria delavayi* Franch. | | | |
| *Paris quadrifolia* Linn. | root | acrid and bitter with cold nature | (41) |
| *Polygonatum cyrtonema* Hua | root | sweet with mild nature | |
| *Polygonatum kingianum* Coll. et. Hemsl. | | | |
| *Polygonatum macropodium* Turcz. | | | |
| *Polygonatum roseum* (Ledeb.) Kunth. | root | bitter with cool nature | |
| *Polygonatum sibiricum* Redoute | root | sweet with mild nature | |
| *Polygonatum verticillatum* (L.) All. | root | bitter with cool nature | |
| *Trillium tschonoskii* Maxim. | root | sweet and acrid with warm nature | |
| *Trillium camtschaticum* Pall. | | | |
| *Veratrum album* L. | rhizome | --- | (36) |
| *Veratrum lobelianum* Bernh. | root and shoot | bitter and acrid with cold nature | (7) |
| *Veratrum nigrum* L. | root | acrid and bitter with cold nature | |
| *Vertatrum viride* Ait. | rhizome | --- | (36) |
| Amaryllidaceae | | | |
| *Curculigo orchioides* Gaertn. | root | acrid with warm nature | (37) |
| *Lycoris radiata* (L'Her.) Herb. | shoot | acrid with warm nature | |

| | | |
|---|---|---|
| Taccaceae | | |
| *Tacca plantaginea* (Hance) Prenth. | root | bitter with cool nature |
| Dioscoreaceae | | |
| *Dioscorea caucasica* Lypski | root | bitter with mild nature (?) |
| Zingiberaceae | | |
| *Curcuma aromatica* Salisb. | root | acrid and bitter with warm nature |
| *Curcuma longa* L. | | |
| Musaceae | | |
| *Musa basjoo* Sieb. et. Zucc. | root | sweet with cold nature |
| Orchidaceae | | |
| *Luisia morsei* Rolfe | whole plant | acrid and bitter with mild nature |

Table 2.1.2 The ten largest families of hypotensive plants.

| Family | no. of genera | no. of species |
|---|---|---|
| Compositae | 24 | 36 |
| Apocynaceae | 12 | 17 |
| Leguminosae | 11 | 17 |
| Labiatae | 10 | 10 |
| Rubiaceae | 9 | 13 |
| Ranunculaceae | 8 | 21 |
| Liliaceae | 7 | 19 |
| Menispermaceae | 7 | 12 |
| Umbelliferae | 6 | 7 |
| Berberidaceae | 4 | 14 |

Table 2.1.3 The five largest superorder of hypotensive plants

| Superorder | no. of genera | no. of species |
|---|---|---|
| Rannunculiflorae | 26 | 57 |
| Asteriflorae | 26 | 39 |
| Gentianiflorae | 21 | 41 |
| Lamiiflorae | 20 | 27 |
| Rosiflorae | 18 | 27 |

Table 2.1.4 The classification of the Chinese medicinal plants by their flavors

| Flavor | no. of species | percentage |
|---|---|---|
| Acrid | 100 | 22.62 |
| Sweet | 113 | 25.67 |
| Bitter | 189 | 42.77 |
| Sour | 20 | 4.52 |
| Salty | 13 | 2.94 |
| Bland | 7 | 1.58 |

Table 2.1.5 The classification of the Chinese medicinal plants by their natures

| Nature | no. of species | percentage |
|---|---|---|
| Cold | 103 | 34.33 |
| Cool | 48 | 16.00 |
| Hot | 3 | 1.00 |
| Warm | 78 | 26.00 |
| Mild | 68 | 22.67 |

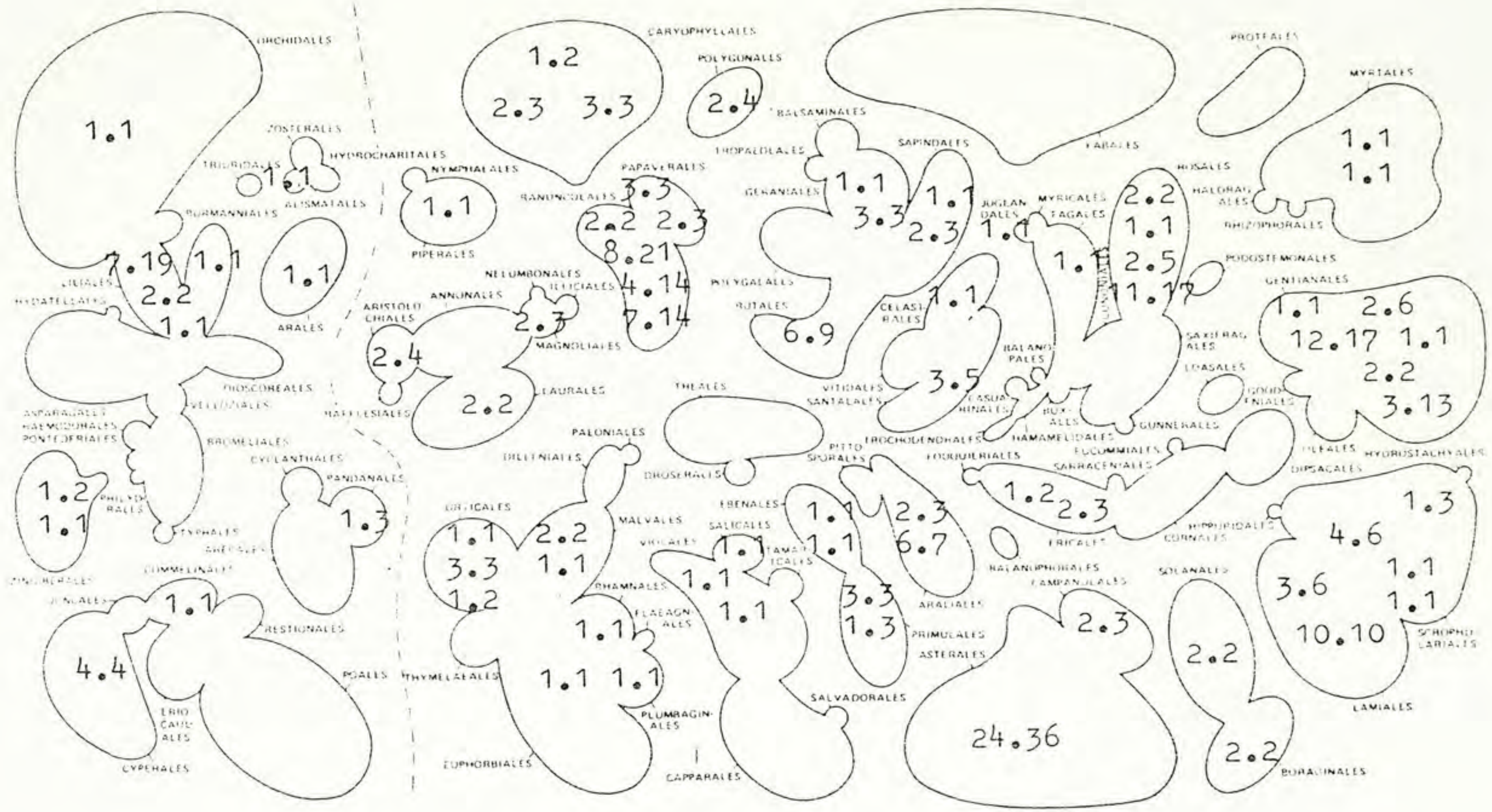


Fig. 2.1.1 Dahlgren's system of classification of angiosperms used to demonstrate the distribution of hypotensive plants (each number represents a single family, and N.M=no. of genus and no. of species)

# SECTION TWO

# HYPOTENSIVE ACTIVE PRINCIPLES IN MEDICINAL PLANTS

The therapeutic properties of Chinese medicine can be traced back to some unique and specific biomolecules in the plants. To distinguish these biologically active compounds with the inactive structural phytochemical components, they are usually known as the active principles of the herbal drugs. The isolation, purification, characterization and synthesis of these active principles are the ultimate goal for the phytochemists who work on medicinal plants. When these become available, pharmacologists then perform indepth investigations on the drug actions and look for possible clinical applications.

As in all the plant materials, the medicinal plants contains many different groups of chemicals. They include proteins, amino acids, lipids, saccharides, organic acids, tannins, quinones, lactones, coumarins, isocoumarins, chromone derivatives, lignans, glycosides, terpenes, volatile oils and alkaloids (1,42). Although active principles have been identified in almost every group of these chemicals, alkaloids and glycosides are the most popular groups.

The Alkaloids (Structure I - XVI)

Many hypotensive principles have been isolated. The most famous one is reserpine (I), an indole alkaloid, which was first isolated from the rootbark of Rauwolfia serpentina

Benth. in 1952 (43). From that time onward, numerous works have been done to isolate reserpine from other *Rauwolfia* species, such as *R. vomitoria* Afzel., *R. verticillata* (Lour.) Baill. and *R. yunnanensis*. The former one contains reserpine up to 1.7%, even more than the amount obtained from *R. serpentina* (4,24). The *Rauwolfia* species are also rich sources for other alkaloids: many hypotensive alkaloids such as yohimbine (II), rescinnamine, reserpiline, ajmalicine (III) and naumitorine were isolated from their roots and leaves (44,45). In China, the alkaloid extracts from *R. verticillata* (Lour.) Baill. and *Rauwolfia vomitoria* Afzel are now commercially available under the trade mark Verticilum and Reseninum respectively, for the treatment of hypertension (46).

Hypotensive alkaloid is not the gift only for *Rauwolfia*, but also for other apocynaceae. From *Catharanthus lanceus*, for example, the well-known hypotensive agent yohimbine was isolated. Akuammidine, an indole derivative, which has a hypotensive effect of weaker but longer lasting than yohimbine has been isolated from the seed of *Picralima nitida* (Stapf.) Th. & H. Dur. (24). Hypotensive steroid alkaloids which is derived from holarrhenine (IV) or from pregnane (V), such as holarrimine, holaphyllamine and holaphylline, and adenin alkaloids, triacanthine (VI) have been found in *Holarrhena* floribunda (Don) Dur. & Schinz. var. floribunda (24). Indole alkaloids, eburnamonine, eburnamine and hunterine, which have strong and lasting hypotensive action have been extracted from the root and stem bark of Hunteria species (24). Voacamine, voacangine, voacorine, vobtusine and tabersonine (VII) have been isolated from Voacanga africana Stapf. and V. bracteata Stapf. (VIII). Vincamin has been also obtained from Vinca minor L. (24).

Since alkaloids are quite widely distributed in the plant kingdom, the hypotensive alkaloids are expected to be found in other families too. Indeed, the bark of Pausinystalia johimbine (Schum.) Pierre ex Beille (Rubiaceae) has been reported contain yohimbine, mesoyohimbine and yohimbinine as well as corynanthine, allyoyohimbine and ajmalicine (24). Corynanthine has been isolated from Corynanthe pachyceras Schum. (Rubiaceae) and rhynchophylline (IX), mitraversine, and mitraphylline (X) has been found in Mitragyna spp. (Rubiaceae) (24,47).

The roots of Cryptolepis sanguinolenta (Lindl.) Schltr. (Periplocaceae) contain a quinoline-derived indole alkaloid, cryptolepine, which can produce a marked and durable hypotension (48). Eserine was obtained from the seeds of Physostigma venenosum Balfour (Fabaceae) (49). Thalctrum alkaloids like thaliadine, adiantifoline and thaliadanine were obtained from the root of Thalictrum minus (Ranunculaceae). They possess a powerful and prolonged hypotensive effect (2 mg/kg) in dogs, cats and rabbits (50). Pyridine alkaloids, carpine, which can reduce blood pressure in small doses has been reported in the young leaves of *Carica papaya* L. (Caricaceae) (51). Furthermore, heliotrine (XI) from the seed of *Heliotropium indicum* (Boraginaceae) reportedly produces a transient hypotension in anesthetized dogs (36).

Some well-known hypotensive alkaloids are obtained from Menispermaceae. Dauricine (XII), an isoquinoline alkaloid extract from the root of *Menisperum dauricum* D.C., has been reported to have hypotensive action in anesthetized cats (26). Tetrandrine (XIII), the active principle of *Stephania tetrandra* S. Moore, possesses a marked hypotensive effect and is now used clinically (52). Dimethylcycleanine bromide which is the δ-amino derivative of cycleanine (XIV) isolated from *Stephania epigea* Diels. It is now used for control hypotension in anesthesia during surgery (53).

A cactus alkaloid, $N^a$, $N^a$-Dimethylhistamine is obtained from *Echinocereus triglochidiatus* Engelm. var. neomexicanus (Standley) Standley ex W.T. Marshall (Cactaceae) and is the hypotensive principle (31). Tetramethylpyrazine XV, the active principle of *Lingusticum wallichii* French., which are generally used in the treatment of brain blood deficiency, has been demonstrated to possess hypotensive action in anesthetized dogs (54). Furthermore, an isoquinoline alkaloid, berbamine hydrochloride (XVI) which is isolated from *Berberis poiretii* and is generally present in berberidaceae, has been demonstrated to produce hypotensive responses in cats, dogs and rabbits (55).

## *The Glycosides* (Structure XVII - XX)

The second major group of the hypotensive principles isolated from plant is glycoside. It is also well-known for its cardiotonic and haemolytic properties. Puerarin (XVII), a flavanoid glycoside obtained from the root of *Pueraria lobata* (Willd.) Ohwi (Leguminaceae), can produce a mild depressor effect in hypertensive patients (56). Isoquercitrin (XVIII) which is isolated from the leaves of *Diospyros kaki* (Ebenaceae) has been shown to have hypotensive property (6). Gomita *et al* reported that the pennogenin tetraglycoside (XIX) obtained from *Paris quadrifolia* Linn. produced hypotensive responses in rats (41).

Olive leaves, *Folia oleae* (Burseraceae), contain a bitter glycoside - oleuropein (XX). This iridoid glycoside possesses a marked antihypertensive and antiarrhythmic action (7). Another glycoside, vernonin, isolated from the root of *Pernonia colorata* (Willd.) Drake (Compositae) produces a marked fall in blood pressure in cat and dogs when injected intravenously (24). Furthermore, there is pachysiphine, a hypotensive aminosteroid glycoside from *Tabernaemontana pachysiphon* Stapf.

(Tabernaemontaneae) (24).

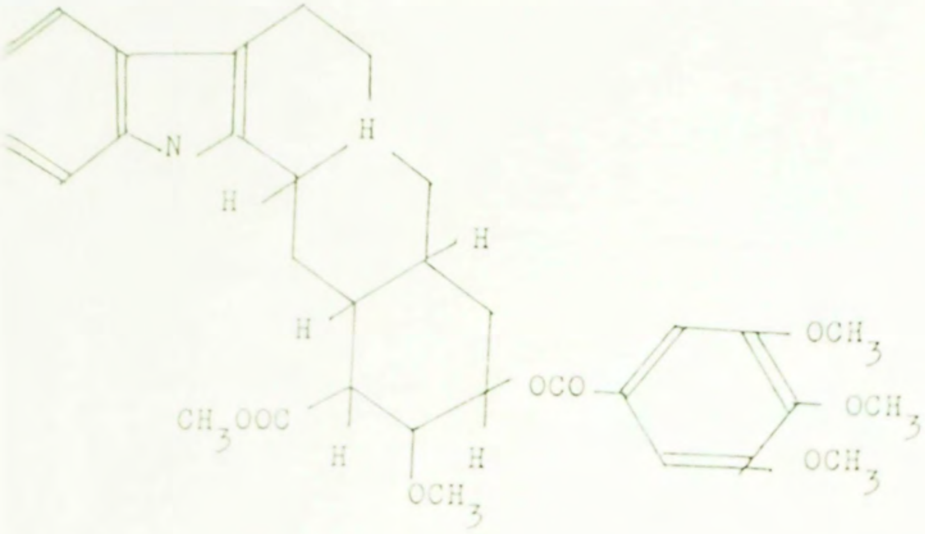
Others (Structure XXI - XXV)

Hypotensive active principles from other groups of chemicals are also identified. From the rootbark of Morus alba L. (Moraceae), a well-known hypotensive herb, come kuwanon G, H (XXI), moracehin A (XXII) and C (XXIII) (6). They are flavanoid derivatives and produce hypotension effects in rats and rabbits. The flavanoid sum called crataemon obtained from the blossoms and leaves of Crataegus monogyna, exercises a slight, short-term hypotensive effect (4). Armillarisin A (XXIV), a coumarin derivative, obtained from the ethanol extract of the culture medium of a fungus, Armillariella tabescen (Scop. ex Fr.) Sing. produces a depressor response in anesthetized dogs (57).

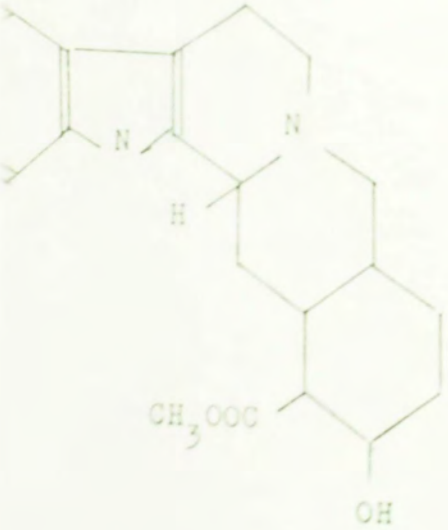
Complex molecule as polysaccharide was identified as the hypotensive principle of the lichen, Dermatocapon miniatum (L.) Mann. (19). On the other hand, simple molecules as allicin (XXV), diallyl disulphide oxide, from Allium sativum L. (Amaryllidaceae) is also responsible for the hypotensive action (7). It is interesting to notice that the common neural transmitter, gamma aminobutyric acid (GABA), has been isolated from Astragulus dasyanthus Pall. (Leguminosae) which is therefore hypotensive (7).

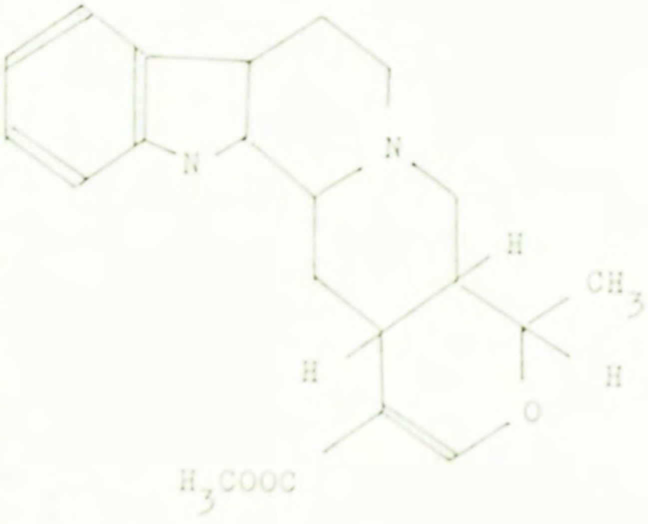
Thus, hypotensive effects of the Chinese medicines are due to the presence of such a wide spectrum of chemicals in the plants ranging from large and complex molecules to simple and small molecules.

## ucture of the Active Hypotensive Principles



(I) reserpine

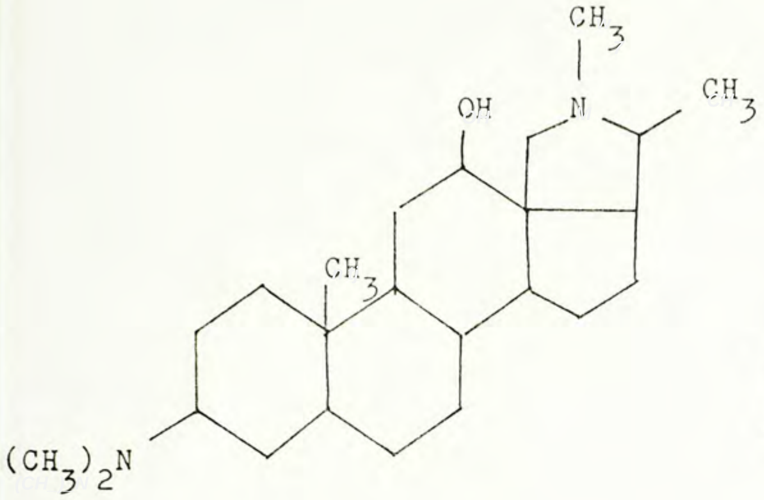




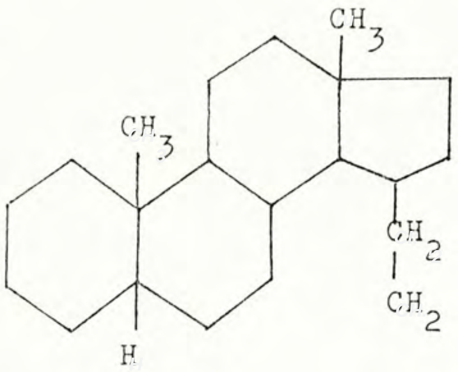
(II) yohimbine

(III) ajmalicine

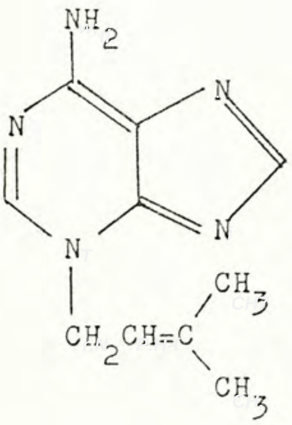
Structure (cont.)



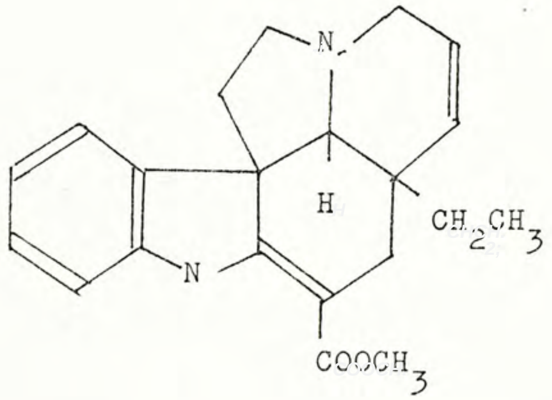
(IV) holarrhenine



(V) 5β-pregnane

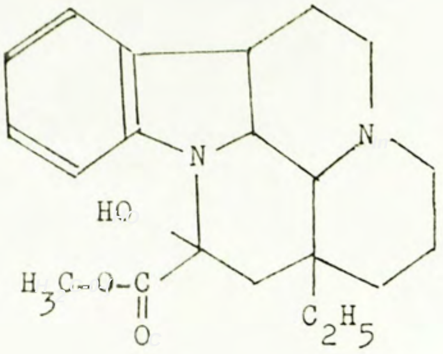


(VI) Triacanthine

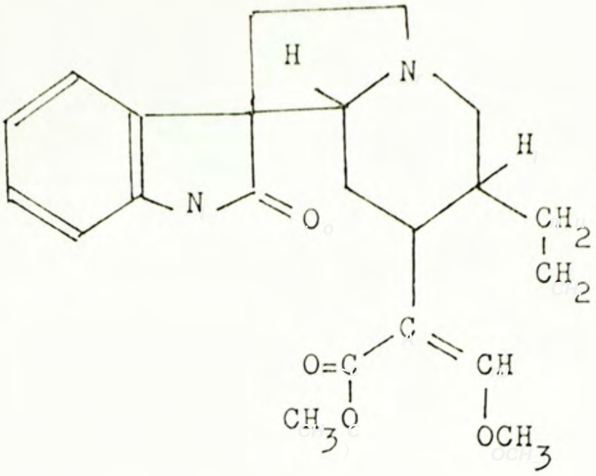


(VII) tabersonine

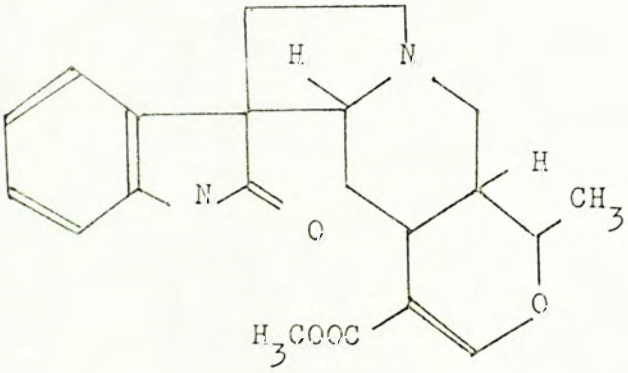
Structure (cont.)



(VIII) vincamin

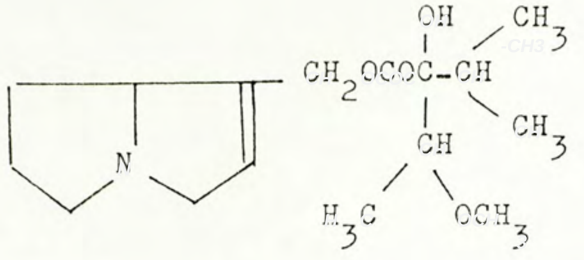


(IX) rhynchophylline

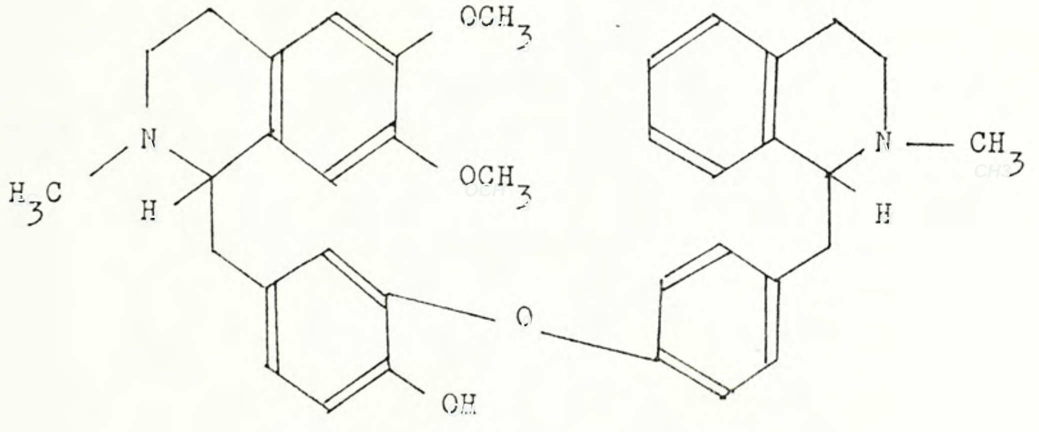


(X) mitraphylline

Structure (cont.)

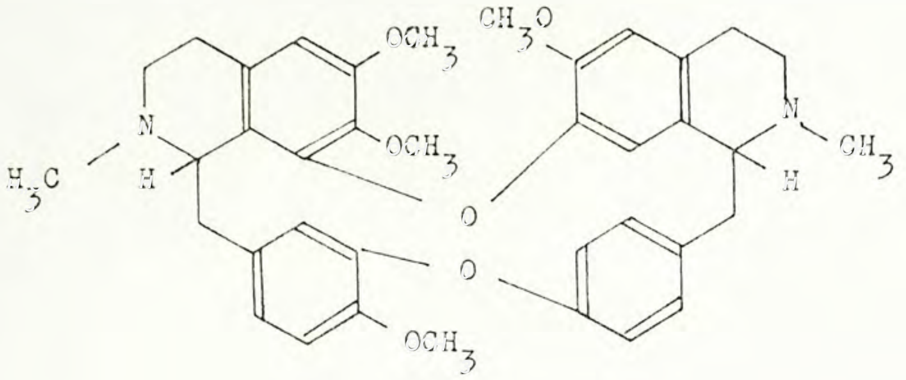


(XI) heliotrine

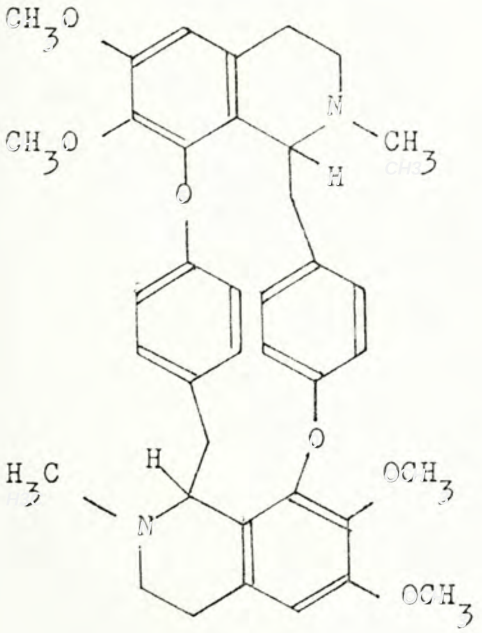


(XII) dauricine

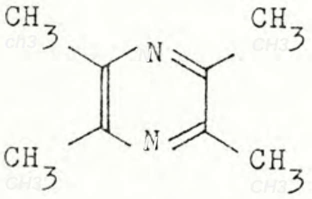
Structure (cont.)



(XIII) tetrandrine

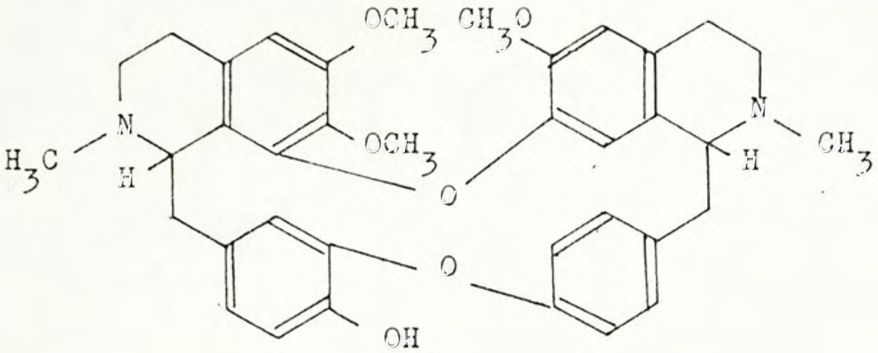


(XIV) cycleanine

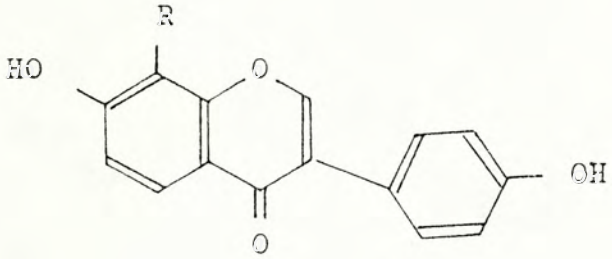


(XV) tetramethylpyrazine

Structure (cont.)



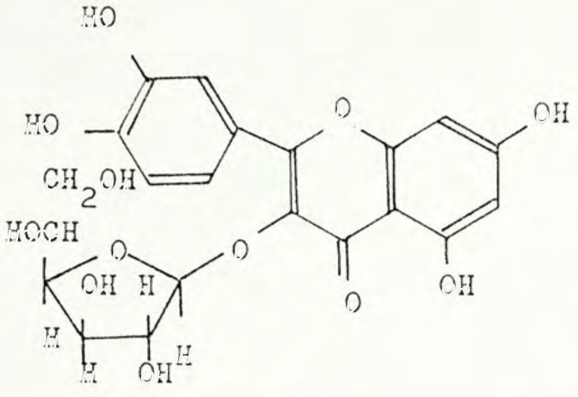
(XVI) berbamine



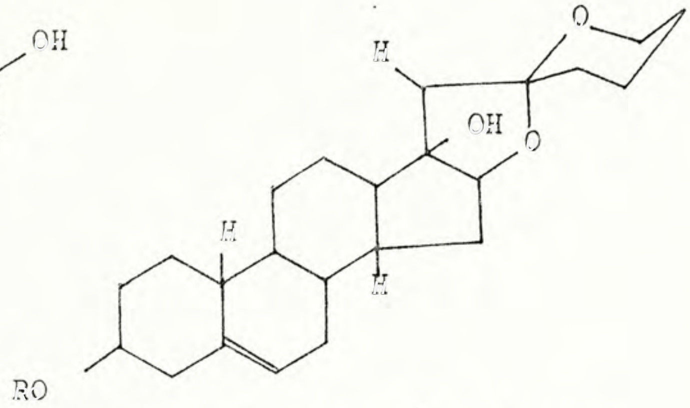
R = D-glucopyranosyl group

(XVII) puerarin

Structure (cont.)

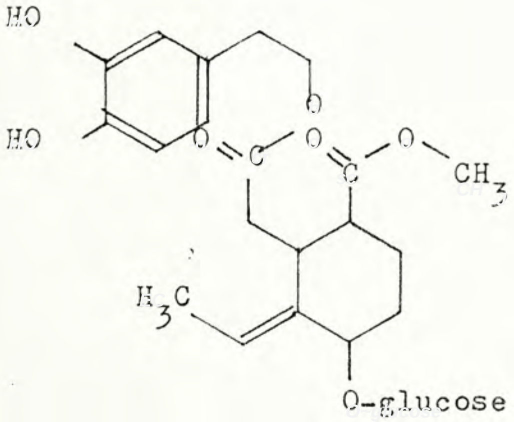


(XVIII) isoqercitrin



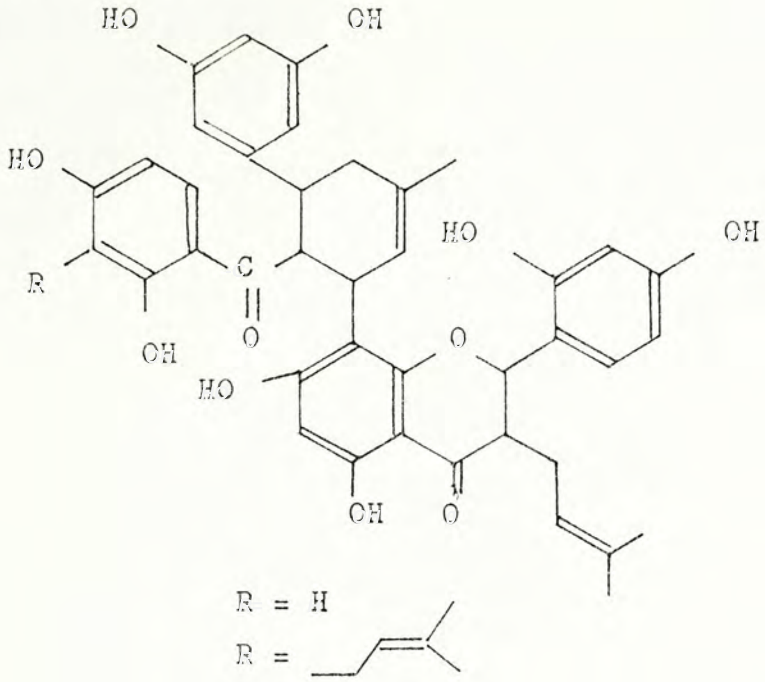
R = -β-D-glu.pyr$^2$- -rha.pyr
|
α-L-rha.pyr
|
α-L-rha.pyr

(XIX) pennogenin tetraglycoside (Tg)

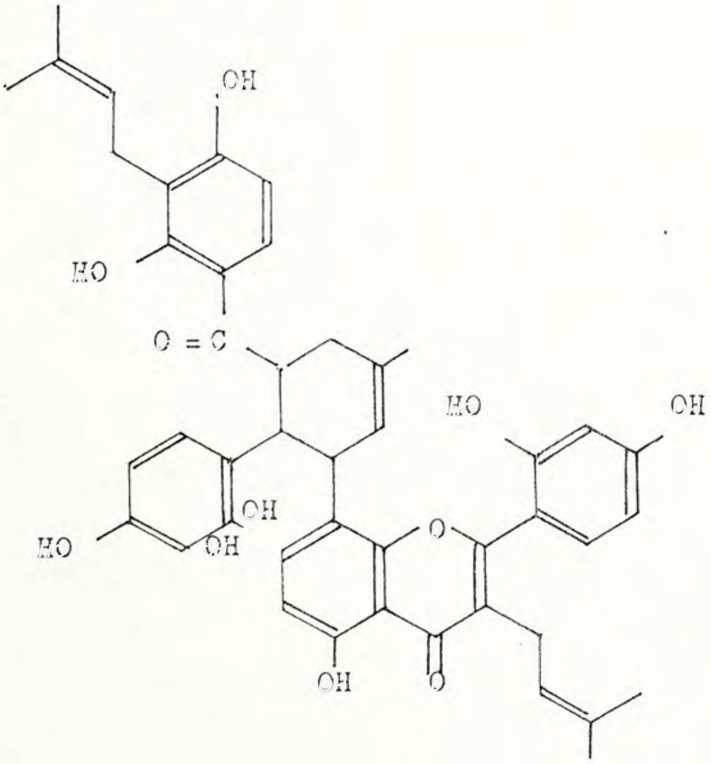


(XX) oleuropein

Structure (cont.)

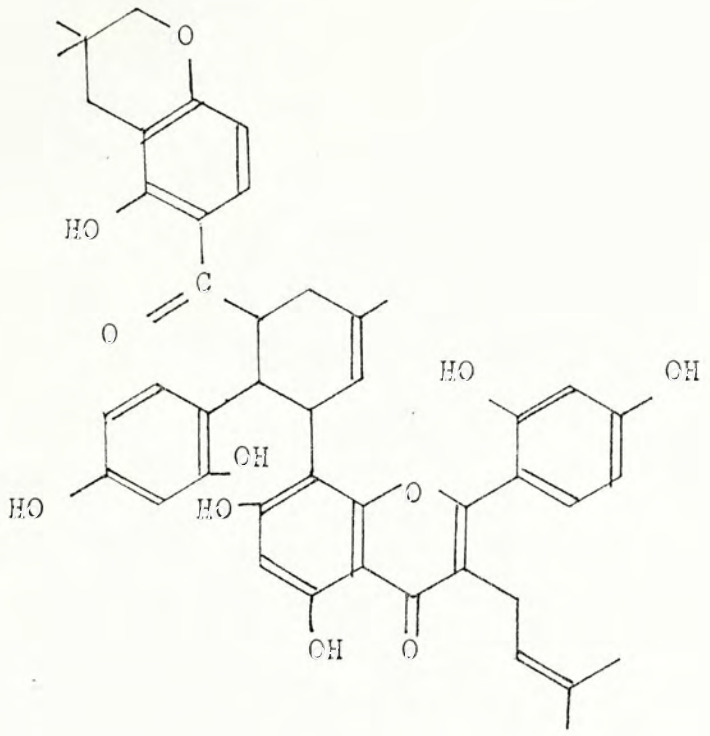


(XXI) kuwanon G, H

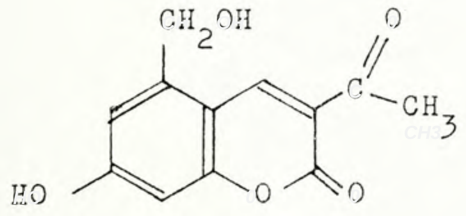


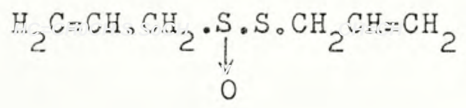
(XXII) moracehin A

Structure (cont.)



(XXIII) moracehin C





$H_2C{=}CH.CH_2.\underset{\substack{\downarrow\\ O}}{S}.S.CH_2CH{=}CH_2$

(XXIV) armillarisin A

(XXV) allicin

# SECTION THREE

# HYPOTENSIVE ACTIONS OF THE MEDICINAL PLANTS AND SOME KNOWN ACTIVE PRINCIPLES ISOLATED FROM THEM

The blood pressure of an animal is determined by its cardiac output and the peripheral resistance. Thus, we can expect any drug that reduces the cardiac output and/or induces vasodilatation will produce a hypotensive effect. A hypotensive drug may act through the nervous system or directly on the vascular smooth muscle. Hypotensive drugs that act on the nervous system include: sedatives that have a depressant effect on the CNS, sympatholytics that are antagonistic to adrenalin, parasympathomimetics that simulate the effect of acetylcholine, and ganglioplegics that can paralyse the nerve cells at the ganglion level.

The action mechanisms of the hypotensive Chinese medicines and their active principles (see section 2) are outlined below:

(A) Active Hypotensive Principles

1) Reserpine is among the most well studied. It depletes the storage of the catecholamine and serotonins in the nerve cells and the adrenal medulla by antagonizing the uptake of of the norepinephrine and dopamine by chromaffin granules. The depletion of catecholamine leads to a fall in blood pressure, due to the decrease on the vasomotor tone and bradycardia (58). Furthermore, reserpine also enhances the arterial responses to vasodilators such as acetylcholine, isoproterenol, histamine,

nitroglycerin and cyclic nucleotides (59). This enhancement may play a part in the reserpine-induced hypotension.

2) Yohimbine, exerts its action by antagonizing the $\alpha$-adrenoceptors. It has a pronounced prejunctional selectivity for the $\alpha_2$-adrenoceptors. It has been demonstrated by the blockade of the prejunctional inhibitory effect of clonidine on the tachycardia evoked by sympathetic nerve stimulation in dogs, at lower doses than those required for blocking the pressor responses to clonidine, noradrenaline, adrenaline, or phenylephrine (60,61).

3) Berbamine produces the depressor response by acting on the CNS and the vascular smooth muscle. This action on the CNS has been shown in cats by intravertebral artery injection. The dose required to produce a depressor response in this preparation was higher than that injected through the femoral or carotid artery. The vasodilatating effect was shown in rat by the hindlimb perfusion techniques (55).

4) The hypotensive action of tetradrine, the active principle from *Stepharia tetrandra* S. Moore is attributed to the decrease in the peripheral resistance and cardiac activity (52). The cardiovascular effect of tetradrine can be enhanced by -antagonist. It is believed that tetrandrine exerts its action by

inhibiting the $Ca^{2+}$ influx into the cardiac muscle cells (62,63).

5) Dauricine, an alkaloid structurally similar to tetrandrine relaxes the norepinephrine preconstricted aortic helical strip of normotensive and the kidney-type hypertensive rats, but it is not antagonistic to $\alpha$-adrenoceptors. The CNS may also play some role in the hypotensive effect, because injection through the vertebral artery produces a fall in blood pressure at a much smaller dose (26). In another study, dauricine relaxed the adrenaline, potassium and noradrenaline preconstricted aortic strips of rats and rabbits. It shifted the dose-response curves of noradrenaline, potassium chloride and calcium chloride to the right. Its action is similar to that of tetrandrine, that is, inhibits the $Ca^{2+}$ entry to the vascular smooth muscle cells (27).

6) Pennogenin tetraglycoside (Tg), extracted from *Paris quadrifolia* Linn. produces a marked fall in the blood pressure of mice, and this reduction in blood pressure is not affected by the pretreatment with atropine and physostigmine. Furthermore, it has a cardiac stimulating effect in the isolated frog heart (41).

### (B) Hypotensive Crude Plant Extracts

1) *Angelica sinensis* is a well-known Chinese medicinal plant. Its water extract can produce a depressor response in anesthetized or conscious dogs. The depressor response is mainly ascribed to the reduction of the peripheral resistance and is mediated through the acetylcholine and histamine receptors (33). *Angelica sinensis* was shown to increase the $Rb^{88}$ uptake in the cardiac muscle by improving the coronary blood flow and by dilating the small arterioles in the heart (32).

2) *Eucommia ulmoides* is commonly known as Tu-chung in chinese. Pharmacological studies showed that the hypotensive effect of its alcohol extract is not mediated through adrenceptors or cholinergic receptors. The central nervous system and the autonomic nervous system do not seem to play any role, since spinal cord transection, ganglion blockade with hexamethonium bromide and vagotomy can not abolish the depressor response. Rat hindquarter perfusion and helical strip studies show that the hypotensive action is due to the reduction in the peripheral resistance by vasodilatation (21).

3) The alcohol extract of the root of *Panax notoginseng* (Burk.) F.H. Chen, which is a close relative of *Panax ginseng*, exhibits a hypotensive action. In anesthetized cats, it produces a depressor response and reduces the heart rate. *In situ* experiments showed that the extract could stimulate

vasodilatation in rabbit kidney, ear and hindquarter (29). It also increases the blood flow rate in the coronary artery (30).

4) The vasodilatory effect of the flower of *Carthamus tinctorius* L. has been studied. The alcohol extract induced vasodilatation in the isolated preparations of guinea-pig posterior extremities and rabbit ears. In experiments on the rabbit aortic strips, *Carthamus* was found to antagonise the vasoconstricting effect of noradrenaline. So, it is believed that the vasodilatatory effect of Carthamus is due to its interference on the α-adrenoceptors (40).

5) The cardiovascular actions of volatile and non-volatile fractions of *Valerina officinalis* L. var. Latifolia Miq. have been examined in rabbits. Both fractions produce hypotensive responses. The volatile fraction exhibits a relaxing effect on the vascular smooth muscle, but the non-volatile fraction causes vasoconstriction. On the other hand, the non-volatile fraction produces a marked bradycardia, while the volatile fraction only produces a slight reduction in heart rate. Thus, the hypotensive effect of the volatile fraction is mainly due to vasodilatation and that of the non-volatile is ascribed to its cardiac action (39).

6) Ethanol extract of Linderae umbellata Ramus shows a central depressing effect in mice via the CNS. It decreases the spontaneous movement and prolongs the duration of hexabarbital-induced sleep. Furthermore, it shows a vasodilating effect on the rabbit peripheral blood vessels and a negative inotropic action on the isolated rabbit heart (25).

7) The mechanism of hypotensive action of Terminalia arjuna has been studied in anesthetized cats and dogs. The pressor effect of the norepinephrine injection and the electric stimulation of the splanchnic nerve were not affected by the extract. Thus, the hypotensive effect is not due to the blockade of autonomic ganglia, adrenergic neurone and peripheral adreoceptors. However, the carotid occlusion response can be inhibited by the drug. This hypotensive effect of Terminalia can also be partially inhibited by bilateral stellate ganglioectomy. It was confirmed by intraventriclar and intravertebral injection that the depressor response is mainly of central origin (28).

The above pharmacological studies only answered a part of the question of how the hypotensive medicinal plants might work. A large portion of the hypotensive plants remains unexamined. It is important not only to see how they work, but also to evaluate their therapeutic values. Will they become the "break through" drugs in cardiovascular disease one day? This should remain for the future work to answer.

# CHAPTER THREE

# EXPERIMENTAL WORK

# SECTION ONE

# THE STUDY OF THE HYPOTENSIVE EFFECT OF FOUR PLANT EXTRACTS

Plants with putative hypotensive actions are distributed unevenly in the plant kingdom (Fig. 2.1.1). In this preliminary study, members from four different families were chosen. These are *Calendula officinalis* L. (Compositae), *Acacia catechu* (L.) Willd. (Leguminosae), *Clematis chinensis* Osbeck (Ranunculaceae) and *Sargassum fusiforme* (Harv.) Setch. (Sargassaceae). The first three are gymnosperms and the last one is an algae.

These four Chinese medicinal plants were chosen because 1) they belong to families which contain a large number of plants with hypotensive action, 2) their hypotensive actions based on available data are still obscure, and 3) they are readily available in Hong Kong.

The properties of the four medicinal plants are reported as follows:

1) The flower of *Calendula officinalis* L. has a bland flavor with a mild nature. The water extract of this plant is traditionally used for cooling the blood and stop bleeding. Intravenous injection of the flower extract produce positive inotropism and negative chronotropism (64).

2) The whole plant of *Sargassum fusiforme* (Harv.) Setch., has a salty flavor with cold nature. It is used for the treatment of acrofula, goiter, abdominal mass, edema, beri-beri

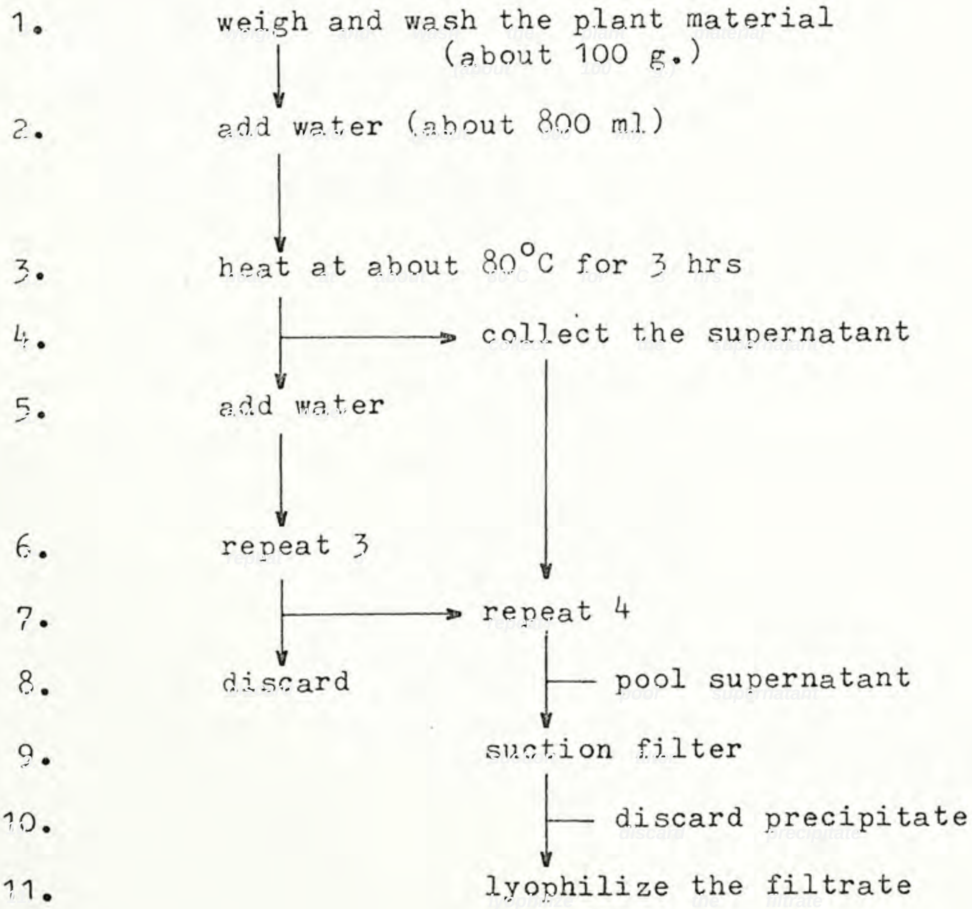
and swollen testis (65).

3) The root of Clematis chinensis Osbeck has a salty flavor with warm nature. It is taken for the treatment of arthalgia, beri-beri, malaria, tetanus and tonsillitis (66).

4) Acacia catechu (L.) Willd. has a bitter taste with a cold nature. The water extract is taken for treating ulcerative gingivitis, aphthae and pharyngitis (67).

## MATERIALS AND METHODS

Hai er cha (Acacia catechu (L.) Willd.), hai zao (Sargassum fusiforme (Harv.) Setch.), wei ling xian (Clematis chinensis osbeck) were purchased from local Chinese drug stores, and jin zhan ju (Calendula officinalis L.) was grown in the green house of Biology Department, the Chinese University of Hong Kong. Since herbal medicines are traditionally taken in the form of aqueous solution, the water extracts of these plants were prepared for examination. The procedures were outlines as follows:


1. weigh and wash the plant material (about 100 g.)
2. add water (about 800 ml)
3. heat at about 80°C for 3 hrs
4. collect the supernatant
5. add water
6. repeat 3
7. repeat 4
8. discard; pool supernatant
9. suction filter
10. discard precipitate
11. lyophilize the filtrate

Animal test

Male Sprague-Dawley rats, weighing between 200-400 g were used as the experimental animal. They were anesthetized with an intra-peritoneal injection of 50 mg/kg sodium pentobarbitol (Abbott). The animal was placed in the supine position and the four limbs were secured tightly by electric wires to a surgical board. A vertical incision was made through skin, from the lower jaw to the upper part of the thorax. The trachea was then exposed by separating the stern-hyoid muscle, and was cannulated with a trachea cannula. The tissue around the left carotid artery was cleared and a segment of the vessel was exposed. A ligature was made on the anterior side and the posterior was clamped by a blood vessel clamp. A small cut was made just posterior to the ligature and a PE-50 cannula filled with heparinized saline was inserted and secured with surgical thread. The cannula was hooked up with a pressure transducer (Narco, P-100B) and a Narco Biosystem polygraph, for blood pressure recording. The left jugular vein was also cannulated for intravenous injection (68).

1) Effect of plant extracts

After a 30-min period of equilibration, two bolus injections of plant extracts at the same dose in term of mg of lyophilized powder/kg body weight was given to each rat. The changes in the mean arterial blood pressure (MAP) were recognized as the differences between the steady MAP before and the lowest MAP after injection. The MAP was allowed to return to the resting level between injections and each injection was flushed with 0.3 ml of 0.9% saline. Each dose was tested with 5 rats.

2) Effect of cation contents in the plant extracts

The potassium, calcium and magnesium contents of the four plant extracts were estimated by atomic absorption spectrometry. Solutions containing $KCl$, $CaCl_2.2H_2O$ and $MgSO_4.7H_2O$ amounts of each salt being the equivalent amounts of cation contents in the plant extracts were administered intravenously to the anesthetized rats to ascertain the effect of these injections on the blood pressure. Four rats were used in this experiment.

## Statistics

All data were presented as Mean±S.E.M. Student's t-test was used whenever applicable. The level of significance was P 0.05. Linear regression was used to calculate the $ED_{50}$ of the extracts.

## RESULT

The Sargassum extract (SFE) produced a dose dependent decrease in the blood pressure of the anesthetized rats. The log-dose response curves are shown in Fig. 3.1.1. Tachyphylaxis was apparent at high doses, the responses of the first injection differed significantly ~~with~~ from that of the second injection. The % decreases in the blood pressure following the first and second injection at the maximum dose (30 mg/kg) were 49.4±4.5 and 28.3±2.6 respectively. The time profiles of the depressor responses were shown in Fig. 3.1.2. The maximum decrease in blood pressure at various doses all appeared at about 100 sec after injection. The duration of the response was longer at high dose than low dose, as judged by the MAP 200 sec following injection.

The Calendula extract (COE) also exhibited a hypotensive effect. The effect was dose-related (Fig. 3.1.3). Tachyphylaxis was also observed. The maximum response was obtained at dose of 600 mg/kg with decreases in MAP at two successive injections being 45.33±5.25% and 25.12±3.16%. The duration of the response at this maximum dose was usually very long, lasting more than half an hour. The time profiles of the responses were shown in Fig. 3.1.4. The responses were biphasic, a very drastic but short-lived drop in blood pressure followed by a mild long lasting hypotension. The first drastic drop seemed to be due to respiratory inhibition of the rat. In normal condition, the anesthetized rat breathed with an even rhythm. However, right after the COE injection the rate of breathing slowed down, and even completely stopped temporary at the maximum dose. Respiration resumed in a short time, accompanied with the recovery of blood pressure. Since it was so short lived, only the second half of the response was considered as the hypotensive response of the COE.

The Clematis extract (CCE) showed vasodepressing effects which were dose-dependent (Fig. 3.1.5). The maximum response was 47.04±4.95% decrease in MAP at the dose of 250 mg/kg. The duration of the response was also very long lasting, usually more than half an hour. Only one dose was tested in each rat. The time profiles of the responses were shown in Fig. 3.1.6.

Acacia extract (ACE) produced a log-dose dependent depressor response in rats (Fig. 3.1.7). The dose for maximum response was 80 mg/kg. Tachyphylaxis was apparent at this dosage and the responses of the first and the second injections were 50.26±7.44 and 24.26±2.68% decrease in MAP respectively. The difference was statistically significant. The duration of the responses varied with dosage - the higher the dosage the longer the duration (Fig.3.1.8). The duration of the responses at maximum dose was about an hour.

The linear regression for the dose response curves and the $ED_{50}$ are listed in Table 3.1.1. The r value, thus the slope, of the regression lines are about the same, however, the potencies are different as adjuded by $ED_{50}$. The SFE was the most potent one, while the COE was the least.

The potassium, calcium and magnesium contents of the four plant extracts are shown in Table 3.1.2. The COE had the highest cation content and the ACE the lowest. Changes in MAP following injections of solutions containing equivalent amounts of cations in the plant extracts are presented in Table 3.1.3. The volume of the injected solutions ranged from 0.05 to 0.2 ml. The hypotensive responses produced by these injections usually had a very short duration and lasted for only about 30 sec. However, the injection of solution with cation content equivalent to 400 mg COE/kg killed all four animals with a marked respiratory inhibition.

## DISCUSSION

The present study shows that all four plant extracts tested show hypotensive effect in rats. Although they all produced a maximum decrease of about 45% in blood pressure, their potencies are quite different. They also differ in the duration of their responses. CCE elicits the longest response, and SFD the shortest. It is obvious that tachyphylaxis appears in these responses produced by the extracts, except perhaps *Clematis* extracts for which the second injection had not been tested. It is a mechanism of the body to neutralize the effect of the extracts. But how this mechanism is turned on is not known.

It is peculiar that the injection of COE produced a biphasic response. Since the drop in the blood pressure right after the injection is so drastic, it is not known whether the mild hypotension appears afterward is due to some hypotensive actions of the extract or just a refractory phenomenon after the nose-dive in blood pressure.

A water extract of plant material contains many substances. For instance, various cations which are readily soluble in water are present in the extract. These can affect the cardiovascular system in the rat, e.g. an increase in the calcium ion concentration can cause vasoconstriction by increasing the influx of $Ca^{2+}$ into the smooth muscle cells. An increase in magnesium ion concentration can cause powerful vasodilatation by inhibiting the vascular smooth musale contraction (69,70). A surge in the extracellular potassium ion can produce a vasodilatlation by stimulating the $Na^{+}$,$K^{+}$-ATPase in the sacrolemma to produce a hyperpolarization (71).

The present data show that the hypotensive effects of the plants extracts are not ascribed to the presence of these cations, since the injections of the cation contents equivalent to those of all extracts except the COE, only produced a small decrease in blood pressure. This small and short-lived drop can be explained as an artifact, as it occur right after the injection of the extracts. The cation content of the COE at the maximum dose killed the rats with respiratory inhibition and this might explain the observed phenomenon after COE injection. It should be noticed that the cations content of COE is the highest and the dose for maximum response production is also the highest amount the four extracts. So steps to eliminate the cations are necessary before any examination on its actions can be done.

Legend

Fig. 3.1.1 The hypotensive effect of Sargassum extract (SFE). The initial MAP was 139.33±2.28 mmHg (n=40). * represents significant difference between the first and the second injection at the same dose. Vertical bars represent S.E.M.

Fig. 3.1.2 The time profile of the depressor response in rats after the injections of Sargassum extract (SFE) at the various dosages.

Fig. 3.1.3 The hypotensive effect of the Calendula extract (COE). The initial MAP was 119.10±3.30 mmHg (n=40). * represents significant difference between the first and second injection at the same dose.

Fig. 3.1.4 The time profile of the depressor response in rat after the injections of Calendula extract (COE) at the various dosages.

Fig. 3.1.5 The hypotensive effect of Clematis extract (CCE) The initial MAP was 151.05±3.07 mmHg (n=22).

Fig. 3.1.6 The time profile of the depressor response in rat after the injection of Clematis extract (CCE) at the various dosage.

Fig. 3.1.7 The hypotensive effect of Acacia extract (ACE). The initial MAP was 119.00±2.85 mmHg (n=25). * represents significant difference between the first and the second injection at the same dose.

Fig. 3.1.8 The time profile of the depressor response in rats after the injections of Acacia extract (ACE) at the various dosage.

Fig. 3.1.1

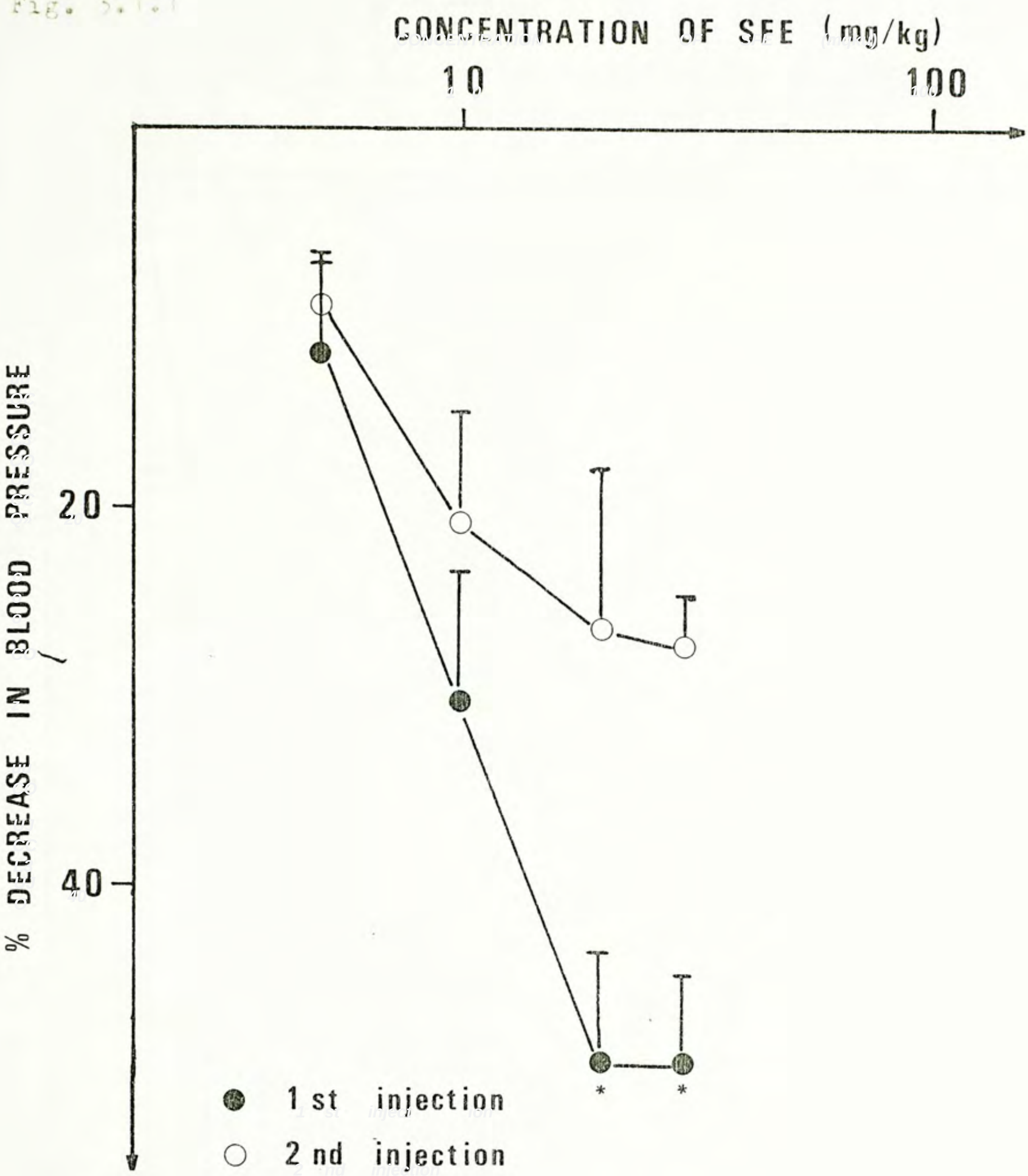

CONCENTRATION OF SFE (mg/kg)
10
100
% DECREASE IN BLOOD PRESSURE
20
40
*
*
● 1 st injection
○ 2 nd injection

Fig. 3.

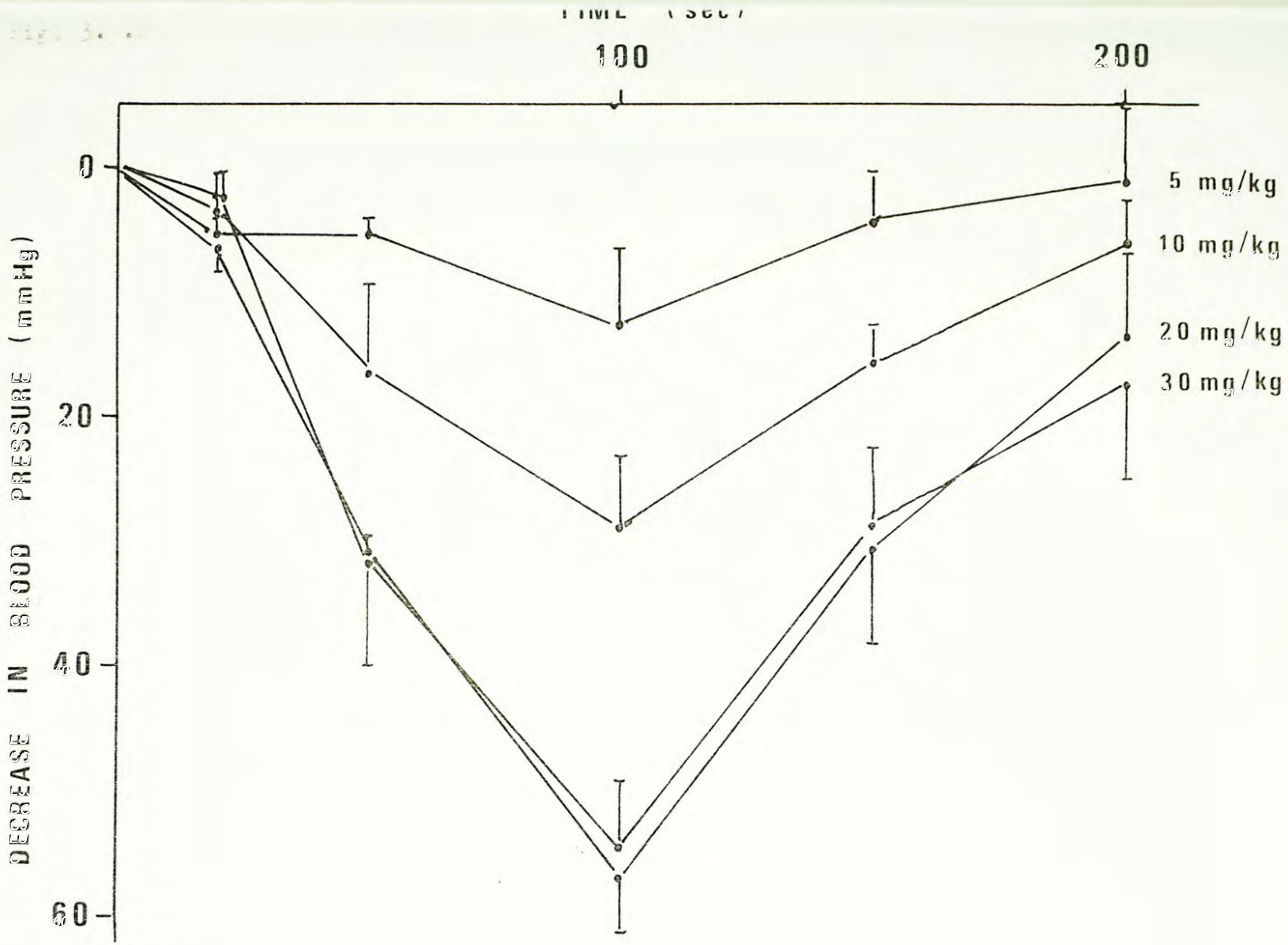
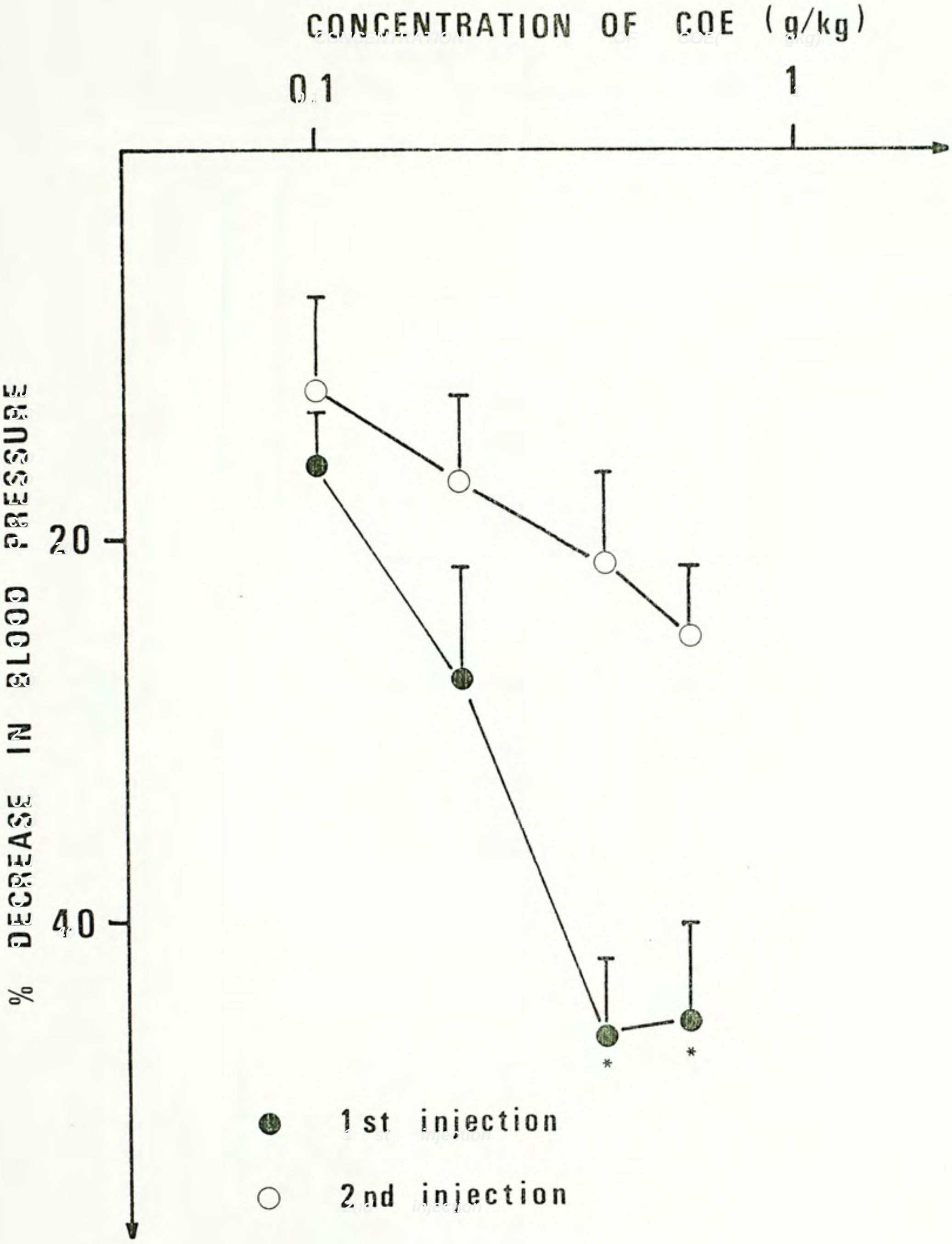

TIME (sec)
100
200
0
20
40
60
DECREASE IN BLOOD PRESSURE (mmHg)
5 mg/kg
10 mg/kg
20 mg/kg
30 mg/kg

Fig. 3.1.3


CONCENTRATION OF COE (g/kg)
0.1
1
% DECREASE IN BLOOD PRESSURE
20
40
*
*
1st injection
2nd injection

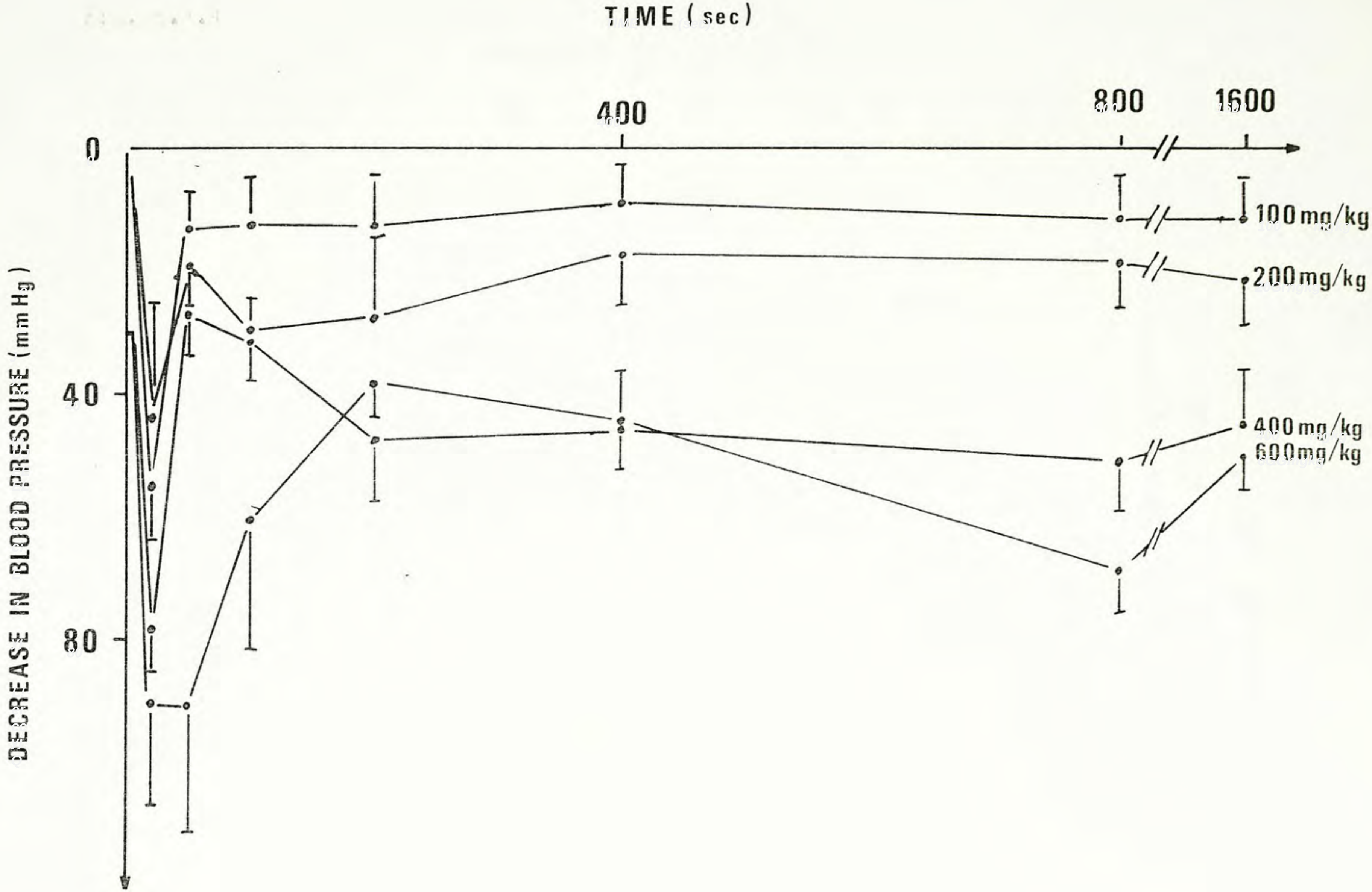
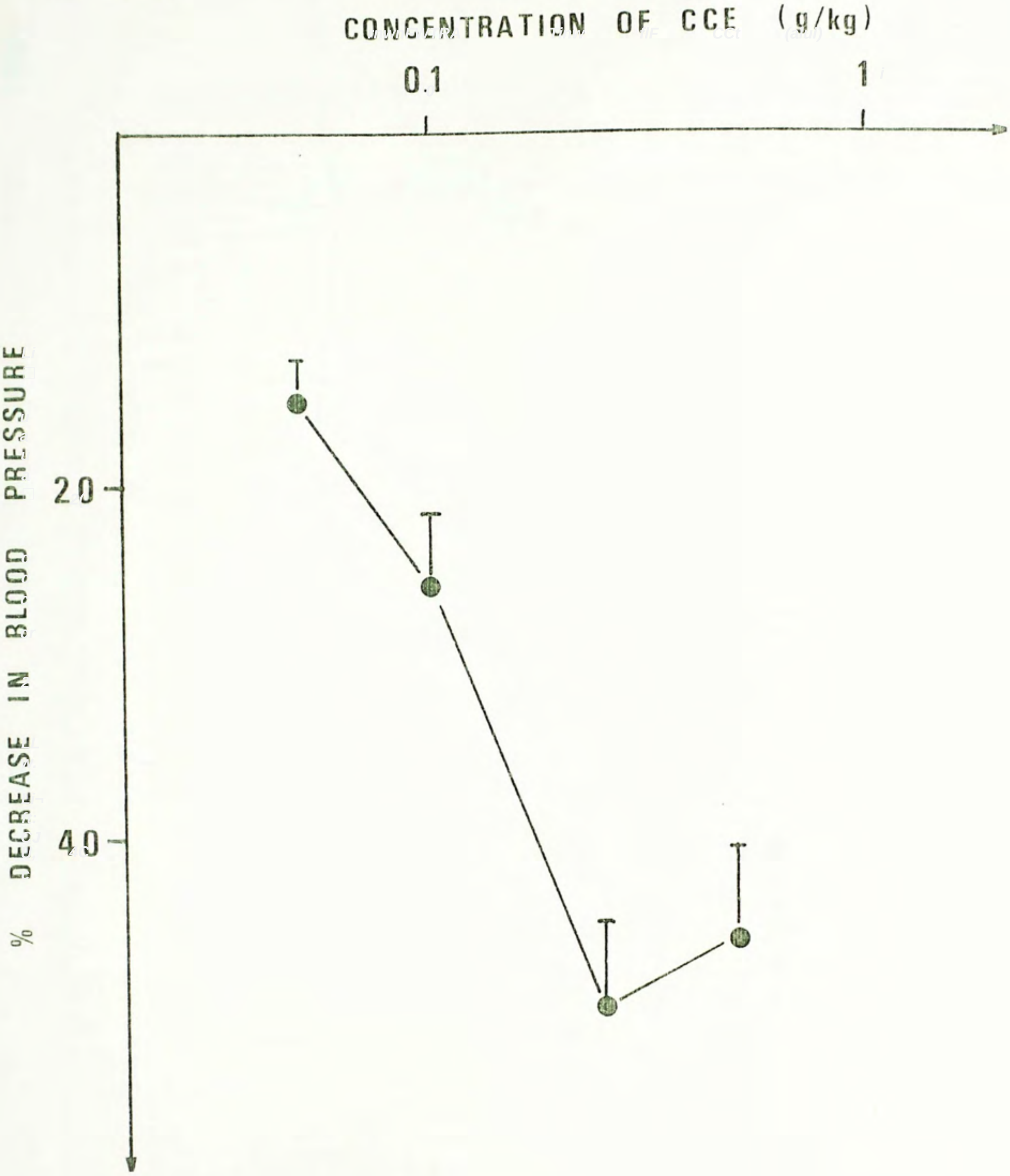

TIME ( sec)
400
800
1600
0
40
80
DECREASE IN BLOOD PRESSURE (mmHg)
100mg/kg
200mg/kg
400mg/kg
600mg/kg

Fig. 3.1.5



CONCENTRATION OF CCE (g/kg)
0.1
1
% DECREASE IN BLOOD PRESSURE
20
40

Fig. 3.1.6

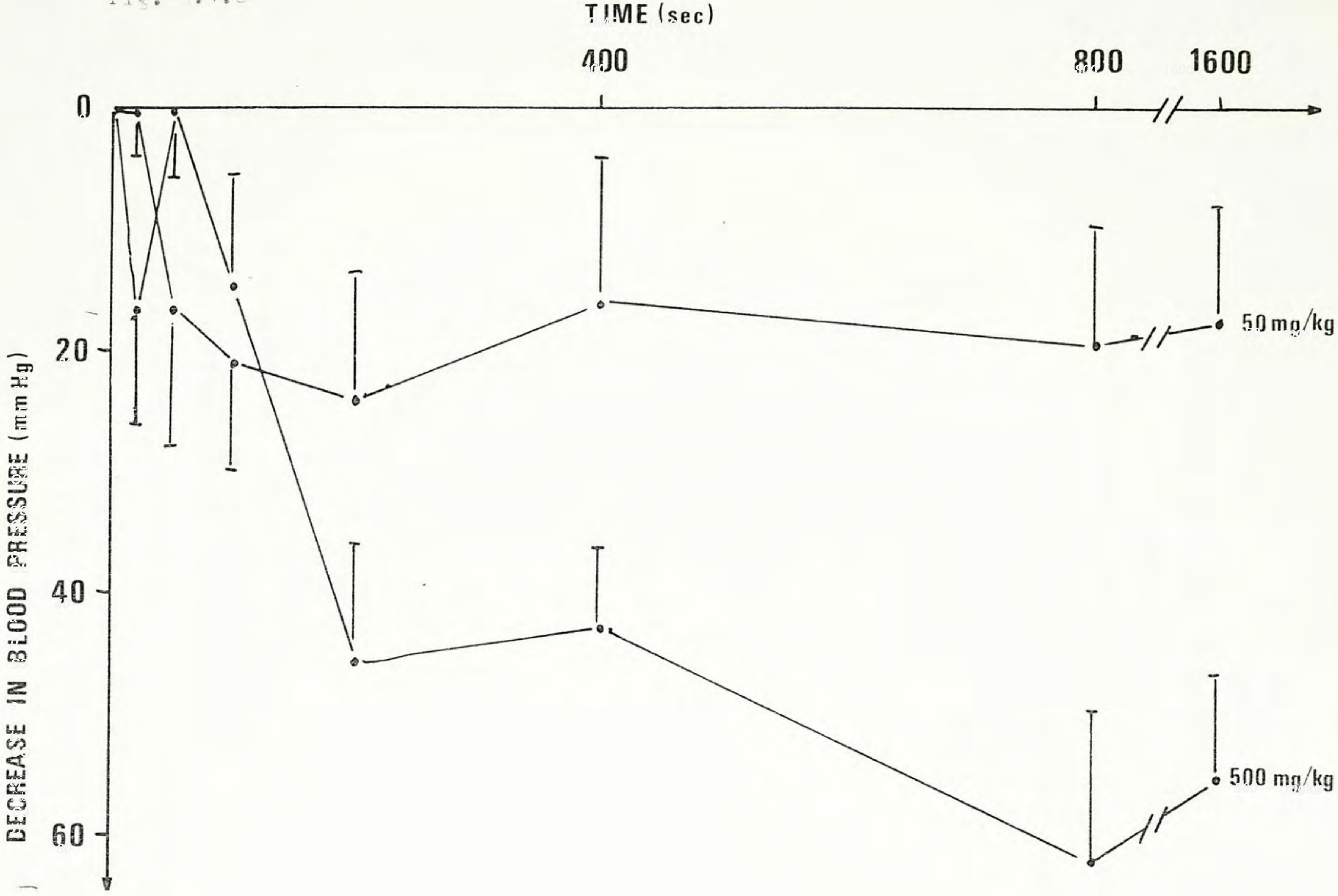
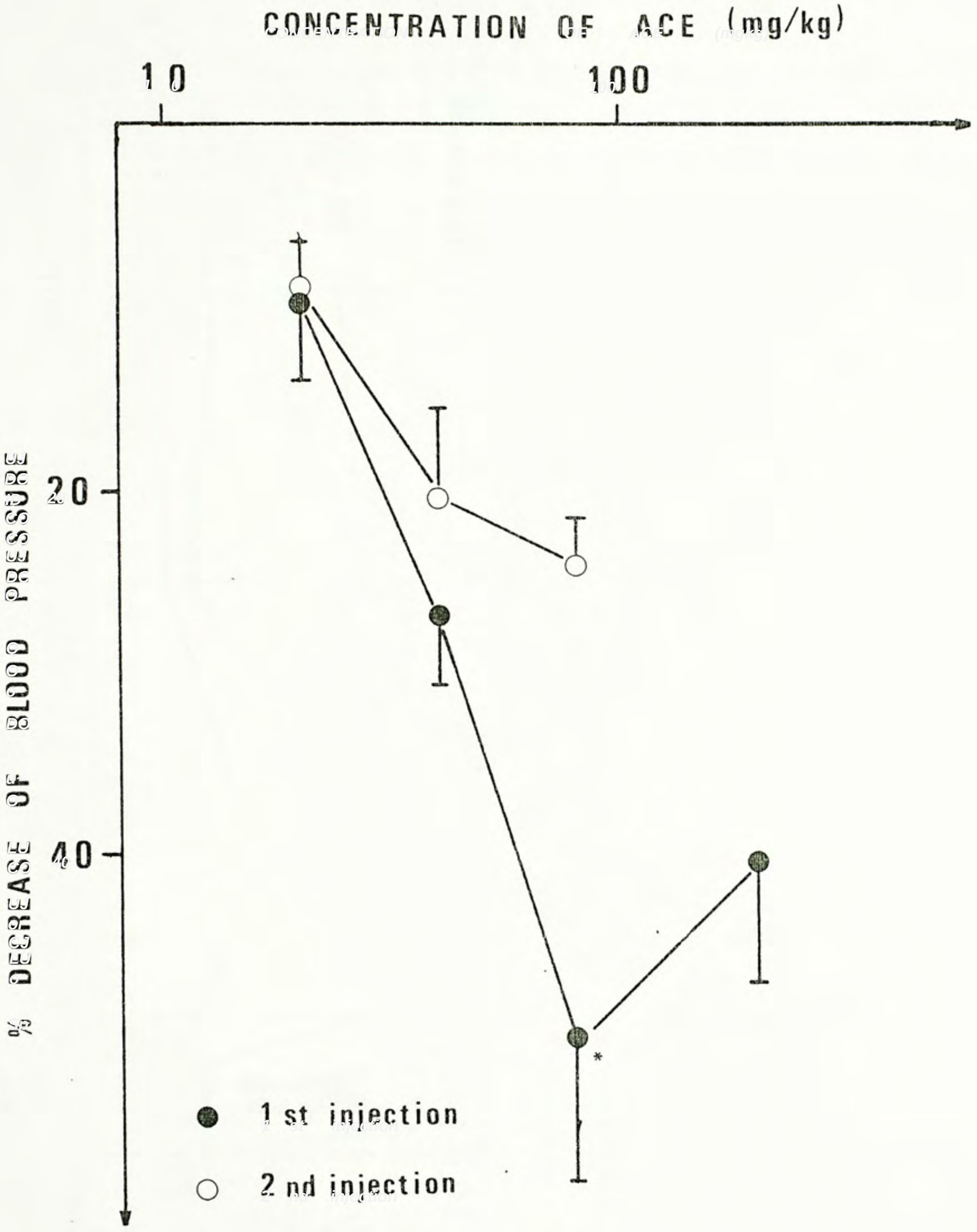

TIME (sec)
400
800
1600
0
20
40
60
DECREASE IN BLOOD PRESSURE (mm Hg)
50 mg/kg
500 mg/kg

Fig. 5.1.9



CONCENTRATION OF ACE (mg/kg)
10
100
% DECREASE OF BLOOD PRESSURE
20
40
*
● 1 st injection
○ 2 nd injection

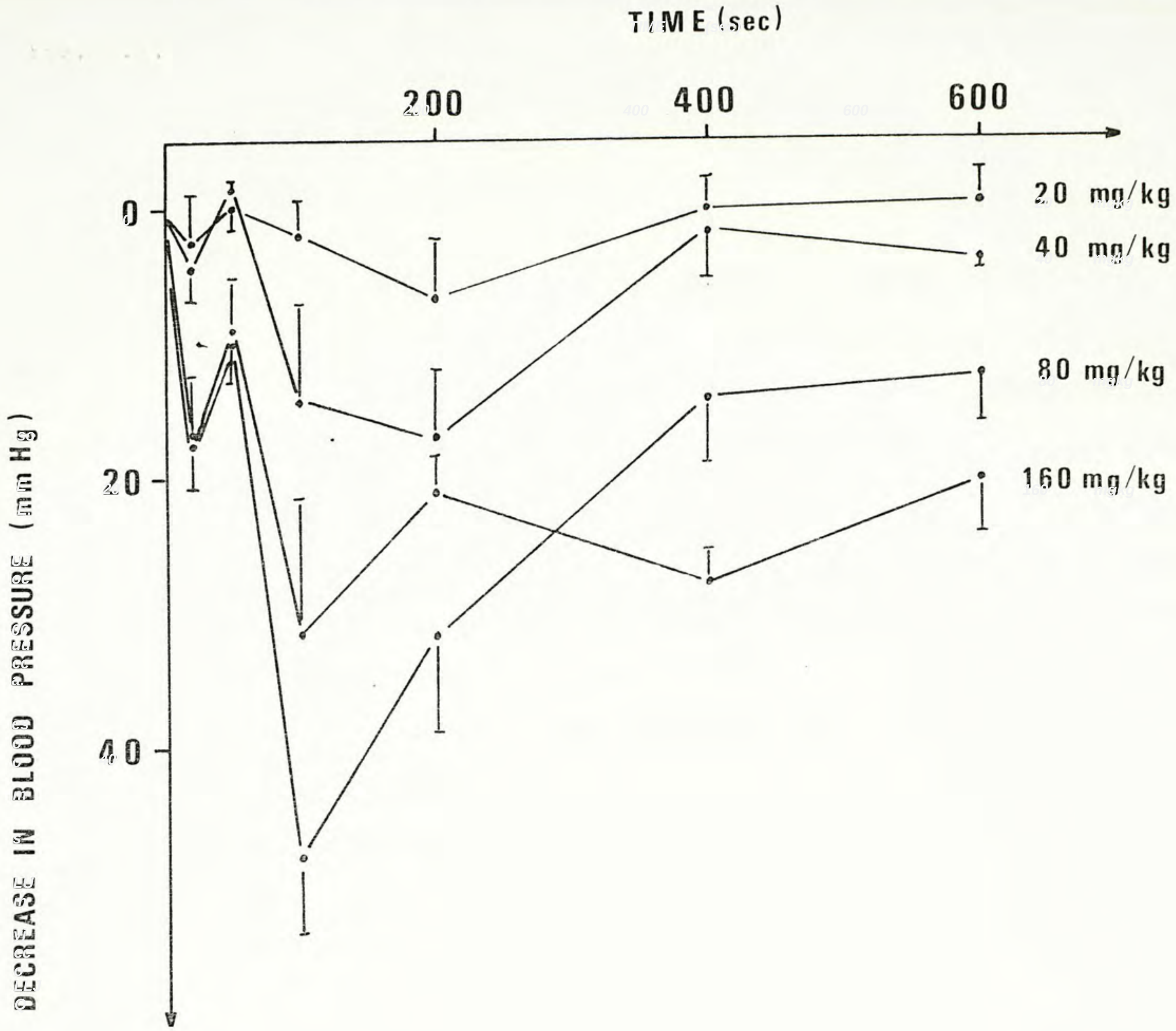

TIME (sec)
200
400
600
0
20
40
DECREASE IN BLOOD PRESSURE (mm Hg)
20 mg/kg
40 mg/kg
80 mg/kg
160 mg/kg

Table 3.1.1 The linear regression of the log-dose response curves and the $ED_{50}$s of the plant extracts in rats.

|  | The regression line |  |  |  |
|---|---|---|---|---|
|  | a | b | r | $ED_{50}$(mg/kg) |
| *Acacia catechu* extract (ACE) | 78.43 | -29.14 | -0.87 | 34.94 |
| *Calendula officinalis* extract (COE) | 83.84 | -21.46 | -0.76 | 145.29 |
| *Clematis chinensis* extract (CCE) | 68.24 | -20.35 | -0.65 | 90.53 |
| *Sargassum fusiforme* extract (SFE) | 31.99 | -27.09 | -0.80 | 17.53 |

Table 3.1.2 The cation contents of the plant extracts.

| | mg/g of plant extract | | |
|---|---|---|---|
| | $K^+$ | $Ca^{2+}$ | $Mg^{2+}$ |
| *Clematis chinensis* extract (CCE) | 3.35±0.01 | 39.49±0.83 | 34.96±0.32 |
| *Calendula officinalis* extract (COE) | 60.19±0.84 | 88.89±0.56 | 63.72±0.45 |
| *Acacia catachu* extract (ACE) | 0.83±0.02 | 10.32±0.02 | 24.83±1.20 |
| *Sargassum fusiforme* extract (SFE) | 7.28±0.01 | 85.17±0.80 | 14.15±1.11 |

Table 3.1.3 The effect of solutions with cations contents equivalents to the maximum doses of the extracts.

| | Decrease in MAP | % decrease in MAP |
|---|---|---|
| CCE (250 mg/kg) | 26.25±2.95 | 20.48±2.40 |
| COE (400 mg/kg) | 116.50±3.23 | 92.10±2.86 |
| ACE (100 mg/kg) | 14.0±1.78 | 10.28±1.42 |
| SFE (20 mg/kg) | 1.75±1.44 | 1.27±1.03 |

The initial MAP of the rats is 129.25±1.59 mmHg (n=16).

# SECTION TWO

# THE STUDY ON THE HYPOTENSIVE ACTION OF <u>ACACIA CATECHU</u>

After the earlier study (section 1), the water extract of Acacia catechu Osbeck was choosen among the four medicinal plants for further study on its hypotensive action. This choice was based on the potency and also the duration of the response. The ACE has a longer duration of response than SFE and is more potent than the CCE. Furthermore, the cations present in the extract do not play any part in the hypotensive action. In this study, attempts were made to delineate whether the action of ACE observed earlier is a direct one, or via various vasoactive substances. Both in vivo and in vitro systems were used. The in vivo systems involved both the anesthetized dogs and rats, and in vitro systems involved the isolated rat tail artery and the isolated rat right atrium.

## MATERIALS AND METHODS

### (A) *In vivo* experiments

### 1) In anesthetized dogs

4 dogs of both sexes, weighing 8 to 12 kg, were anesthetized with an intravenous injection of 30mg of sodium pentobarbitol per kg of body weight. An incision was made in the upper part of the right thigh. A segment of the right femoral artery and vein were isolated from the surrounding tissue and cannulated with polyethylene tubing PE-200. The trachea was also intubated, and the animals were allowed to breathe spontaneously (85). Several bolus injections of different doses of water extract of *Acacia* were given to each dog. Each injection was followed by a wash of 2 ml of 0.9% saline. The arterial blood pressure was recorded and the change in the MAP was determined as described before.

### 2) In anesthetized rats

Male Sprague-Dawley rats weighing between 170-250 g. were anesthetized and prepared as described before (section 1). Several bolus injections of the water extract of *Acacia* at different doses were given to each rat. Each injection was followed by a wash of 0.3 ml of 0.9% saline. 5 animals were tested.

### 3) Pharmacological antagonist studies in rats

The mechanism of the hypotensive property of Acacia extract was studied by using different blockers. Its interactions with the autonomic ganglion transmission, $\alpha$-adrenergic, $\beta$-adrenergic, acetylcholine, histamine-1, histamine-2 receptors and the kinin system were also studied.

Rats were prepared as outlined before. In cases of continuous infusion of blockers, the left femoral vein was cannulated with a PE-50 cannula. Blockers were infused into the animal by a compact infusion pump (Harvard apparatus). Acacia extract at 16 mg/kg body weight was tested during the studies. Each blocker was tested with 5 animals.

a) Autonomic ganglion transmission

Ecolid, which is an autonomic ganglion blocker was injected intravenously at dose of 1 mg/kg body weight to pretreat the rats. After the depressed blood pressure became constant, a bolus injection of Acacia extract was given. The change in MAP was recorded.

b) $\alpha$-adrenoceptor

The effect of the $\alpha$-adrenoceptor blockade on the hypotensive action of Acacia extract was examined. An effective dose of methoxamine (50 $\mu$g/kg), which is an $\alpha$-agonist, was injected intravenously to observe the pressor effect. A dose of phentolamine (2 mg/kg) was then injected slowly to give a α-blockade. As soon as the MAP became steady, the same dose of methoxamine was given again. If the pressor effect was blocked, a test dose of Acacia extract was then given immediately.

c) β-adrenoceptor

A β-agonist, isoproterenol (0.2 µg/kg), was injected intravenously and its vasodepressor effect was observed. A blocking dose of propranolol (2 mg/kg) was then injected and the β-blockade was ensured by testing with the same dose of isoproterenol. Acacia extract was then injected and the change in MAP was recorded.

d) Acetylcholine receptor

Acetylcholine, at dose of 2 µg/kg was injected intravenously to observe its hypotensive response. Rats were then atropinized with 2 mg/kg atropine. The effectiveness of the muscarinic receptor blockade was verified by obtaining a diminished response of acetylcholine at the same dose. A test dose of Acacia extract was then followed.

e) Histamine receptors

A bolus injection of histamine, a powerful vasodepressor was given intravenously at dose of 2 µg/kg to the rat to observe the hypotensive response. Pyrilamine and cimetidine, a $H_1$ and $H_2$ receptor blocker respectively, were then injected together at dose of 10 mg/kg each. The blockade was examined by injecting the same dose of histamine. If the action of histamine was blocked, a dose of Acacia extract was then given immediately.

f) Kinin system

i) The possible interaction between the hypotensive effect of Acacia extract and the kinin system was studied by using a converting enzyme inhibitor, Captopril (SQ14,225) (73). The converting enzyme inhibition was tested by injecting angiotensin I at dose of 40 ng/kg before and after captopril infusion. At first, a test dose of Acacia extract was injected to observe the hypotensive action. Captopril (SQ14,225), 10 µg/min/kg was infused into the rat through the femoral vein at rate of 0.07 ml/min. After at least 30 mins of infusion, the same dose of Acacia extract was given again. The decrease in MAP and also the duration of the response were recorded. In the experiment, the duration of the response was represented by the period of time needed for the 75% recovery of the MAP after the injection of drugs.

ii) The effect of captopril infusion on bradykinin and Acacia extract was studied. Acacia extract and bradykinin (10 µg/kg) were tested separately before and after captopril infusion.

The decrease in the MAP and the duration of 75% recovery were recorded for comparison.

(B) In vitro experiments

1) Isolated rat tail artery

Male Sprague-Dawley rats, weighing 300-400 g were used in the experiment. They were killed by decapitation and an incision was made in the ventral side of the tail. The ventral tail artery was isolated quickly and placed in Krebs Henseleit (K-H) solution of the following composition: 115.0 mM NaCl, 5.0 mM KCl, 25.0 mM $NaHCO_3$, 1.2 mM $NaH_2PO_4$, 2.1 mM $CaCl_2$, 1.2 mM $MgSO_4$ and 11.0 mM dextrose. The solution was continuously aerated by 95% $O_2$ and 5% $CO_2$. The arteries were cleaned of connective and fat tissues and the helical strips were then prepared as described (74,75). A 2 cm strip of rat tail artery was cut under a dissection microscrope at an angle of 45°. The helical strip, 2 mm in width and 3 cm in length, was suspended inside a tissue chamber containing 10 ml of aerated K-H solution which was maintained at 37°C. The two ends of the helical strip were tied by silk threads and connected to the bottom of the tissue chamber and a force displacement transducer (Grass FT03) above. Isometric contractions were recorded on a polygraph (Grass model 79). Before exposure to drugs, the tail artery preparation was equilibrated for 60 min. under a resting tension of 0.7 g. Arginine vasopressin at dose of 2 mM/ml or methoxamine at dose of 0.2 μg/ml were added directly into the chambers to induce vasoconstriction. When a steady tension was achieved, <u>Acacia</u> extract was added to the tissue chamber and cummulative dose-responses were obtained. The entire dose-response curve was done within 20 mins, during which the contractile effect of AVP or methoxamine was not altered. Bradykinin (1 μg/ml) was also tested for comparison. Four successful preparations were used in the experiment.

2) Isolated rat atrium

Male Sprague-Dawley rats, weighing 170-250 g were killed by decapitation. A thoracotomy was performed and the heart was excised rapidly and placed in continuously aerated K-H solution. The atrial tissue was prepared as described (76). The right atrium was isolated and suspended inside a tissue chamber containing 10 ml of aerated K-H solution at 37°C. The two ends of the atrial tissue were tied by silk threads which connected to the bottom of the tissue chamber and a Grass force displacement transducer. Isometric contractions were recorded on a Grass polygraph. The atria were allowed to beat spontaneously and atria with arrhythmical beatings were discarded. Before the administration of drugs, the atrial tissue was equilibrated for 30 min under a resting tension of 1 g. <u>Acacia</u> extract was added directly into the tissue chamber and the atria were washed and equilibrated after each test of drugs. Bradykinin at concentration of 1 µg/ml was also tested for comparison. Six atrial tissue preparations were used in the experiment.

## Statistics

All values are expressed in Mean±S.E.M. Student's t-test are used whenever applicable. The level of significance is P smaller than 0.05. The $ED_{50}$ of the log-dose response curves are calculated according to Fleming et al (77).

## Drugs

Phentolamine (Pegitine HCl) (CIBA), methoxamine (Burroughs Wellcome Co.), isoproterenol HCl (Sigma), propranolol HCl (Sigma), atropine (Sigma), acetylcholine (Sigma), cimetidine (Sigma), pyrilamine maleate (Sigma), histamine dihydrochloride (Sigma), captopril (SQ 14,225) (SKF), angiotensin I (Pennisula), bradykinin (Sigma).

## RESULT

### (A) *In vivo* experiments

#### 1) In anesthetized dogs and rats

ACE produced a hypotensive response in both normotensive dogs and rats. The log-dose response curves are presented in Fig. 3.2.1. In dogs, ACE produced a maximum decrease of 34.3±4.2 mmHg in blood pressure at dose of 40 mg/kg. The $ED_{50}$ was 10.4 (8.9-12.1) mg/kg Mean (95% confidence interval). The MAP of the dogs before each injection was 123.9±3.0 mmHg (n=16).

The maximum response to ACE in rats was a decrease of 39.3 mmHg in MAP at dose of 80 mg/kg. The $ED_{50}$ was 14.1 (9.0-22.2) mg/kg. The MAP of the rats before each injection was 130.6±2.0 mmHg (n=23). There was no significant difference between the $ED_{50}$ of ACE in dogs and rats.

#### 2) Pharmacological antagonist studies in rats

The hypotensive effect of ACE did not seem to act on the CNS. After the administration of a ganglion blocker, ecolid, the hypotensive effect of ACE could still be seen. Ecolid (1 mg/kg) injection caused a decrease of 45.0±7.3 mmHg in MAP and an $ED_{50}$ dose of ACE (16 mg/kg) gave a further decrease of 18.2±1.7 mmHg in blood pressure. Comparing the MAP before and after ACE injection, there was a significant decrease in blood pressure under ecolid induced blockade (Fig. 3.2.2).

Phentolamine blocked the pressor effect of methoxamine (50 µg/kg) significantly, from 34.2±3.0 to 3.8±1.2 mmHg. But it could not block the depressor effect of ACE, which caused a decrease of 44.4±5.3 mmHg in blood pressure after phentolamine induced α-blockade (Fig. 3.2.3). Phentolamine (2mg/kg) itself produced a decrease of 51.6±6.6 mmHg in blood pressure.

The depressor effect of isoproterenol diminished significantly after the administration of propranolol. However, the hypotensive effect of ACE was unaffected and decreased the MAP by 33.8±6.7 mmHg (Fig. 3.2.4).

The depressor response of rats to ACE was not mediated through cholinergic receptors. Atropine, which blocked the hypotensive response of acetylcholine completely, did not affect that ACE which caused a 42.0±5.7 mmHg decrease in MAP (Fig. 3.2.5).

The intravenous injection of combined histamine blockers, pyrilamine and cimetidine, blocked the depressor effect of histamine completely. But the hypotensive effect of ACE was left undisturbed after the injection of these blockers, and produced a depressor response of 43.2±7.2 mmHg (Fig. 3.2.6).

The infusion of captopril caused a decrease in the pressor effect of angiotensin I from 23.0±3.48 to 7.8±2.03 mmHg. The difference was statistically significant. However, captopril did not affect the depressor effect of ACE significantly, although a small increase in response was observable (Fig. 3.2.7a). The response durations before and after captopril infusion were 3.3±0.3 min and 7.0±1.2 min respectively. Thus, the response of ACE was prolonged significantly by captopril infusion (Fig. 3.2.7b).

In the experiment on the effect of captopril on bradykinin and ACE, captopril prolonged the duration of response of bradykinin (1 µg/kg) from 1.3±0.3 min to 7.5±1.2 min, but it did not affect the magnitude of the depressor response. On the other hand, both the magnitude and the response duration were potentiated by captopril infusion (Fig. 3.2.8).

The control value of the hypotensive response of ACE at dose of 16 mg/kg without under the influence of any antagonist or inhibitors was 45.0±7.3 mmHg (n=7).

(B) In vitro experiments

1) Isolated rat tail artery

ACE produced dose-dependent relaxation in the helical strips of rat tail artery (Fig. 3.2.9). The log-dose response curves are shown in Fig. 3.2.10. Two different vasoconstrictors, arginine vasopressin (2 mU/ml) and methoxamine (0.2 μg/ml), were used to preconstrict the arteries. They generated tensions of 0.69±0.03 g and 0.73±0.05 g respectively. The $EC_{50}$ which is defined as the concentration of ACE to reduce half of the preconstricted tension of the helical strips, for the AVP preconstricted strips was 0.051 (0.014-0.183) mg/kg and that for the methoxamine preconstricted one was 0.373 (0.248-0.561) mg/kg. The latter one had a value about seven times higher than the former one, and their difference was significant. Bradykinin (1 μg/ml) induced a transient vasoconstriction of 0.12±0.03 g (n=6), instead of relaxation in the rat tail artery.

2) Isolated rat atrium

The cardiac action of ACE was also studied, it produced both positive chronotropic and inotropic responses in isolated right rat atrium. The responses were dose-dependent and the log-dose response curves for these actions are shown in Fig. 3.2.11. ACE stimulated a maximum increase of 28.3±6.1 beats/min in heart rate at dose of 1 mg/ml. The $EC_{50}$ was

0.144 (0.125-0.166) mg/ml. The normal heart rate before the addition of drugs was 307±5 beats/min. ACE also caused an increase in the atrial contractile force. The concentration for producing a 50% increase in contractile force ($EC_{50\%}$) was 0.570 (0.353-0.926) mg/ml. The initial atrial contractile force before the addition of any drug was 0.300±0.046 g. Bradykinin (1 µg/ml) was also shown to possess positive chronotropic and inotropic actions. It stimulated an increase of 35±3 beats/min in heart rate, and 38.1±8.92% in contractile force.

## DISCUSSION

The present study demonstrated a hypotensive effect of the aqueous extract of Acacia catechu (ACE) in both dogs and rats. The $ED_{50}$s obtained from the log-dose response curves indicate that the hypotensive effects are about same extent in these two different experimental animals.

The reduction in blood pressure by intravenous injection of an extract may of course be due to some non-specific factors other than the specific one. For instance, the concentration of the different ions present in the extract which we have already encountered in the previous section. The histamine release is another non-specific factor that may account for the hypotensive response. Indeed, the direct injection of foreign substances into the blood stream may stimlate histamine release from the mast cells and basophils as an immulogical response or due to the damage of these cells (78). Histamine can induce a depressor response which involve both $H_1$ and $H_2$ receptors (79), and the $H_1$ receptors are the predominant vascular histamine receptors (80).

The present data shows that the combined injection of pyrilamine and cimetidine, specific $H_1$ and $H_2$ antagonist respectively, at doses which can block the effect of agonists (81), do not attenuate the hypotensive effect of ACE. Furthermore, dogs are usually more sensitive to the hypotensive action of histamine than rats, however, the depressor response of ACE does not differ significantly between dogs and rats. The available data suggest that the depressor effect of ACE is independent of histamine release.

The hypotensive effect of ACE does not seem to act on the CNS. It is because the hypotensive effect of ACE still persists after the administration of ecolid, a ganglion blocker, although the response is to a lesser extend. The injection of ecolid produces a drop in blood pressure and it is a characteristic of ganglion blockade. This depressor response is ascribed to the combined effect of dilatation of arteriole and veins (82).

In the present study, it is evident that the depressor effect of ACE is mediated via neither the $\alpha$ nor the $\beta$-adrenoceptors. Phentolamine and propranolol, which can produce $\alpha$ and $\beta$-receptor blockade, do not reduce the hypotensive effect of ACE. The sustained hypotensive state which appears after phentolamine injection is ascribed to the $\beta$-adrenergic vasodilatation probably because of the increase of catecholamine release resulting from the $\alpha_2$-blockade (83).

The possibility of cholinergic receptor mediated hypotension by ACE is also excluded, for the depressor response produced by ACE does not attenuate after the administration of atropine.

The involvement of the renin-angiotensin system and the kinin complexes in the ACE induced response has also been considered in the present study. Infusion of captopril (SQ 14,225), which is an orally active converting enzyme inhibitor (73,84), is found to potentiate the depressor response of ACE by lengthening the duration of the response. The converting enzyme or kininase II, is a peptidyl dipetidase which locates mainly in the lung and kidney (85). It can remove the dipeptide from the C-terminal of peptides or proteins (86). It serves a dual function of converting angiotensin I to angiotensin II and inactivating bradykinin (86). The inhibition of this enzyme by captopril is expected to inhibit the pressor effect of angiotensin I and potentiate the depressor effect of bradykinin due to the decrease in its breakdown. The potentiation of the hypotensive response of ACE after captopril infusion strongly suggests that the depressor response is bradykinin related. As significant reduction in the pressor effect of angiotensin I and significant potentiation of the depressor effect of bradykininwere observed, this confirms that the converting enzyme is effectively inhibited.

One may argue that the hypotensive effect of ACE may be related to the angiotensin system other than the kinin system, for the converting enzyme has a role in both systems. However, captopril infusion in the normotensive subjects do not produce a hypotensive effect as in the situation of activated renin and angiotensin system (86), so the sngiotensin system does not seem to play an important part in maintaining the normal blood pressure. So disturbance of this system in the normotensive animals does not likely produce a rapid response of hypotension. Furthermore, if the hypotensive action of ACE is related to the angiotensin system, the -adrenergic antagonists should have some effect on it. It is because the pressor effect of angiotensin is partially mediated by the -adrenoceptors and should be largely reduced by -adrenergic antagonists (87). However, phentolamine does not appear to affect the action of ACE. This finding suggest that the hypotensive effect of ACE is related to bradykinin than to the angiotensin system.

Up to this step, with reference to ACE's hypotensive effect, some questions as follows are waiting for answers. 1) Is bradykinin the hypotensive principle of ACE, or is it present in the ACE? *In vivo* bradykinin release can be induced by foreign substances, e.g. substances with negative charged surfaces, that can activate Hageman factor (HF) for blood clotting and fibrinolysis (88,89). 2) What is the mode of action of ACE?

Data from the in vitro experiments provide answers to these questions. The ACE can produce vaso-relaxation independent of the kinin release in the experiment of the isolated rat tail artery. The kinin precursor, kininogen, which is present in the blood (90), is absent from the in vitro system. Thus the vaso-relaxation in the rat tail artery must have been induced by some active principles other than bradykinin present in the ACE. But, whether it is the same active substance/s that produce the vasodepressor response and the vasodilatation is unknown. However, vasodilatation certainly contributes an important part in the reduction of blood pressure. The active substance/s in ACE for vasodilatation, if it is the active hypotensive principle, is not bradykinin, because in this study bradykinin induces vasoconstrition on the rat tail artery as in some other vascular smooth muscle preparations (91).

It is interesting to note that ACE is more effective in the relaxation of the vasopressin preconstricted rat tail arteries than the methoxamine preconstricted one. Since these two vasoconstrictors are associated with different receptors for their actions, it may be presumed that the vasopressin activated constriction is more susceptible to the ACE induced vaso-relaxation, and the reason is unknown. The low concentration of ACE for inducing vaso-relaxation in the AVP preconstricted arteries, again excludes the possibility of the cations induced vaso-relaxation (section 1).

Finally, ACE produces positive inotropic and chronotropic responses in the isolated rat atrium. This cardiac stimulating effect of ACE in the _in vitro_ system confirms the presence of biologically active componds in ACE. The active principle may act through the various receptors present in the atrium or affect the stability of the cardiac cell membrane. But it is too early to comment on its cardiac stimulating actions.

From the present data, it can be said with certainty that the hypotensive principle/s present in ACE is/are peptide or protein in nature and can be inactivated by the converting enzyme (peptidyl dipeptidase). This is reasonable because the action of the converting enzyme is not very specific. It can cleave the dipeptide from the carboxyl end of any peptide, if the first amino acid is not a glutamic acid and/or the second one is not a proline. Since there is no report on the presence of the biologically active peptide or protein in _Acacia catechu_, this is the first report on this subject.

In conclusion, the hypotensive effect of ACE is due to the presence of one or more hypotensive peptides or proteins, and this effect is ascribed to vasodilatation. Furthermore, ACE possesses cardiac stimulating effect on both the atrial contractile force and contracting rate.

## Legend

| | |
|---|---|
| Fig. 3.2.1 | The log-dose response curve of the hypotensive effect of ACE on anesthetized dogs and rats. |
| Fig. 3.2.2a | The representative diagram showing the hypotensive effect of ACE after ecolid induced ganglion blockade. |
| 3.2.2b | The effect of ACE after ecolid induced ganglion blockade. * represents significant decrease in MAP of the ecolid pretreated rats after ACE injection. |
| Fig. 3.2.3a | The representative diagram showing the hypotensive effect of ACE after α-adrenoceptor blockade. |
| 3.2.3b | The effect of ACE after phentolamine induced α-adrenoceptor blockade. * represents significant decrease in the pressor effect of methoxamine after phentolamine treatment. |
| Fig. 3.2.4a | The representative diagram showing the hypotensive effect of ACE after β-adrenoceptor blockade. |
| 3.2.4b | The effect of ACE after propranolol induced β-adrenoceptor blockade. * represents significant decrease in the depressor response of isoproterenol after propranolol treatment. |

Fig. 3.2.5a The representative diagram of the hypotensive effect of ACE after cholinergic receptor blockade.

3.2.5b The effect of ACE after atropine induced muscarinic receptor blockade. * represents the significant reduction in the depressor response of acetylcholine after atropine treatment.

Fig. 3.2.6a The representative diagram of the hypotensive effect of ACE after histamine receptor blockade.

3.2.6b The effect of the ACE after pyrilamine and cimetidine induced $H_1$ and $H_2$ receptor blockade. * represents the significant attenuation in the depressor response of histamine after the treatment of histamine blockers.

Fig. 3.2.7a The effect of captopril infusion on the hypotensive effect of ACE.

3.2.7b The effect of captopril infusion on the duration of the response of ACE. * represents significant difference.

Fig. 3.2.8a The effect of captopril infusion on the hypotensive effect of ACE with bradykinin as reference.

3.2.8b The effect of captopril infusion on the duration of the response of ACE, with bradykinin as reference. * represents significant difference.

Fig. 3.2.9 The representative diagram showing the effect of ACE on the a) AVP preconstricted and b) methoxamine preconstricted helical strips of the rat tail arteries.

Fig. 3.2.10 The dose response curve of the vaso-relaxing effect of ACE on the rat tail arteries. The initial tension of the AVP and methoxamine preconstricted helical strips were 0.69±0.03 g and 0.73±0.05 g respectively. Four preparations were used.

Fig. 3.2.11 The dose-response curve of the positive chronotropic and inotropic effect of ACE on the isolated right rat atrium.

Fig. 3.[illegible]

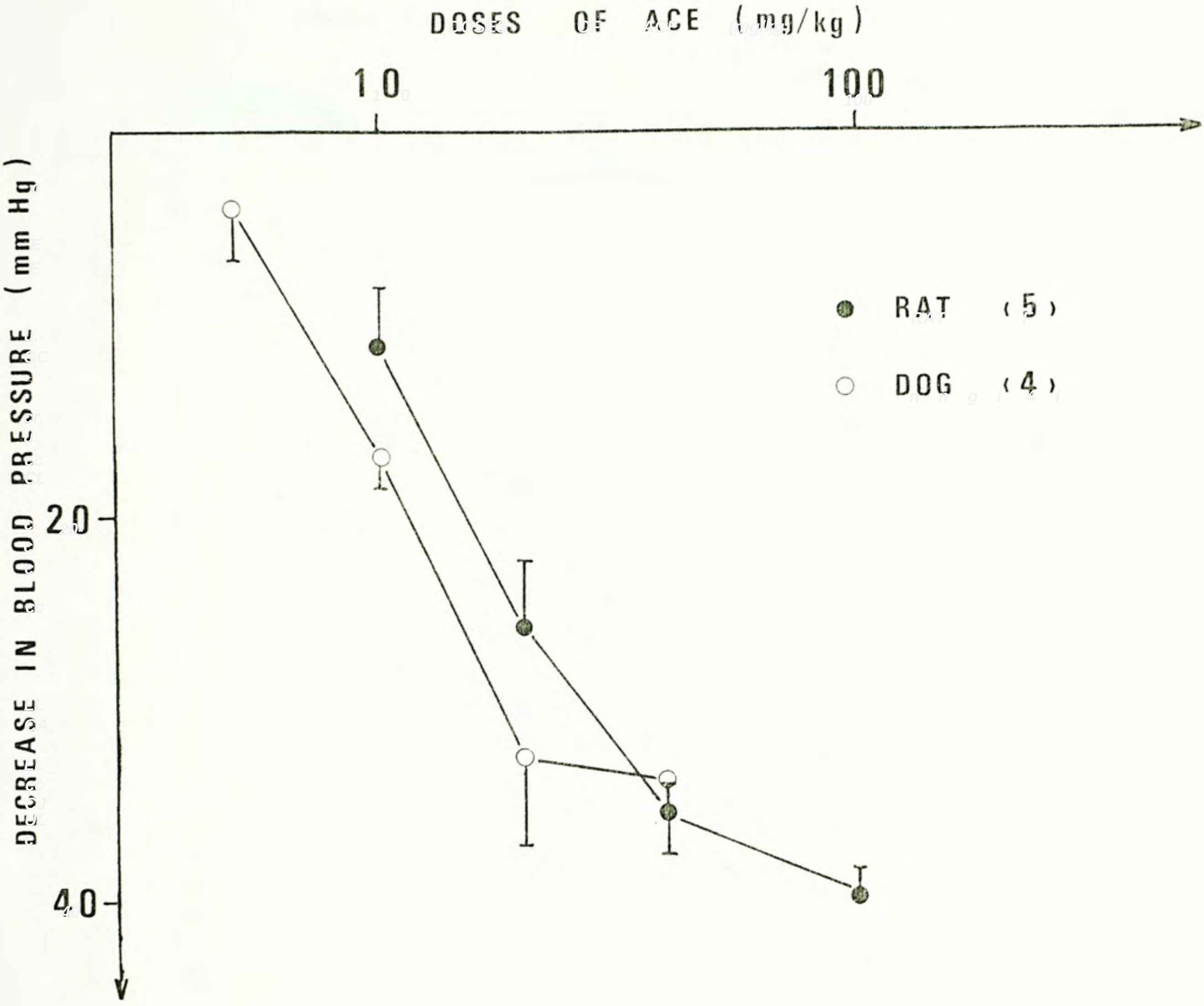

DOSES OF ACE (mg/kg)
10
100
DECREASE IN BLOOD PRESSURE (mm Hg)
20
40
● RAT (5)
○ DOG (4)

Fig. 3.2.2a,b

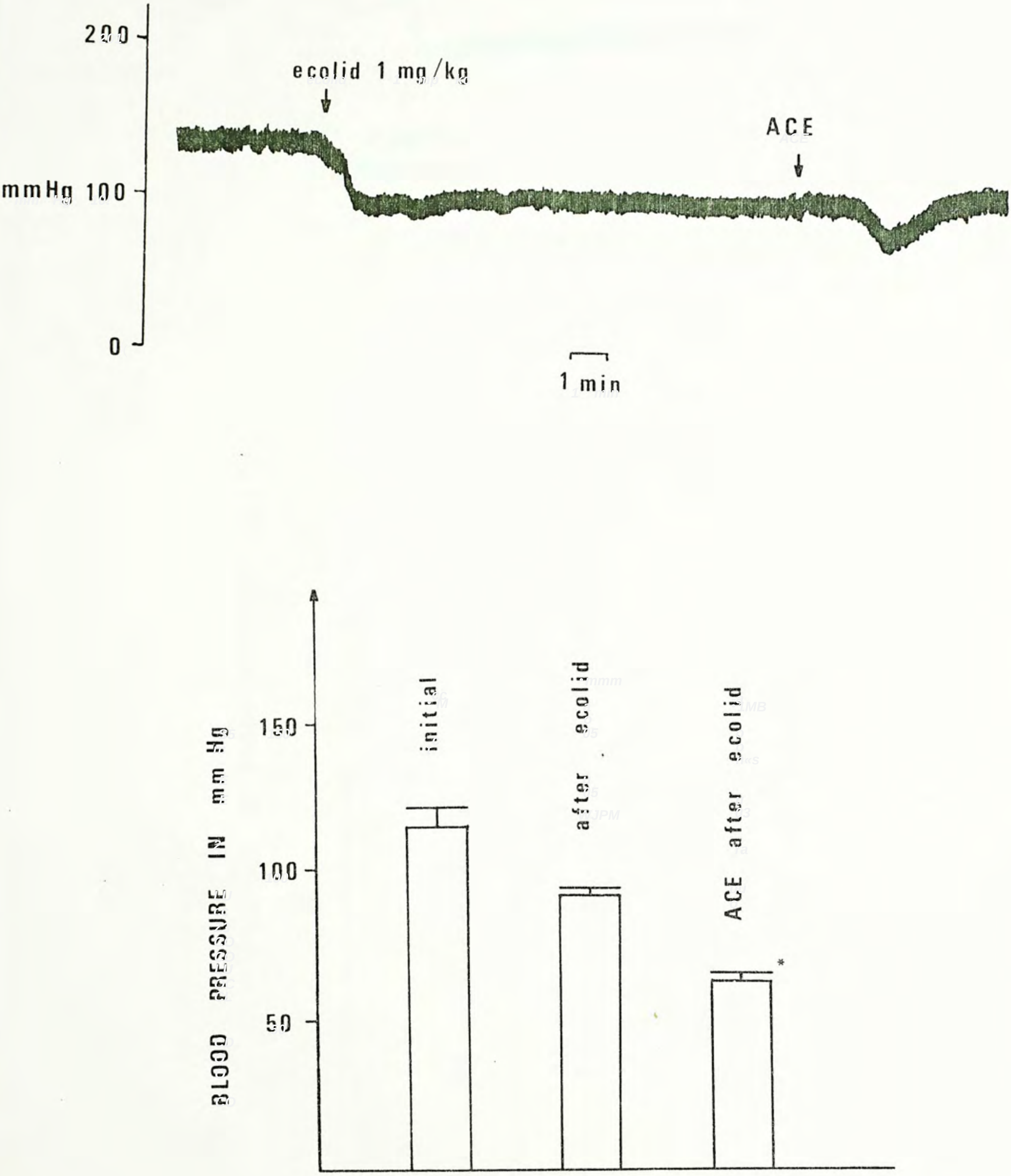

200
ecolid 1 mg/kg
ACE
mmHg 100
0
1 min
BLOOD PRESSURE IN mm Hg
150
100
50
initial
after ecolid
ACE after ecolid
*

Fig. 3.2.3a,b

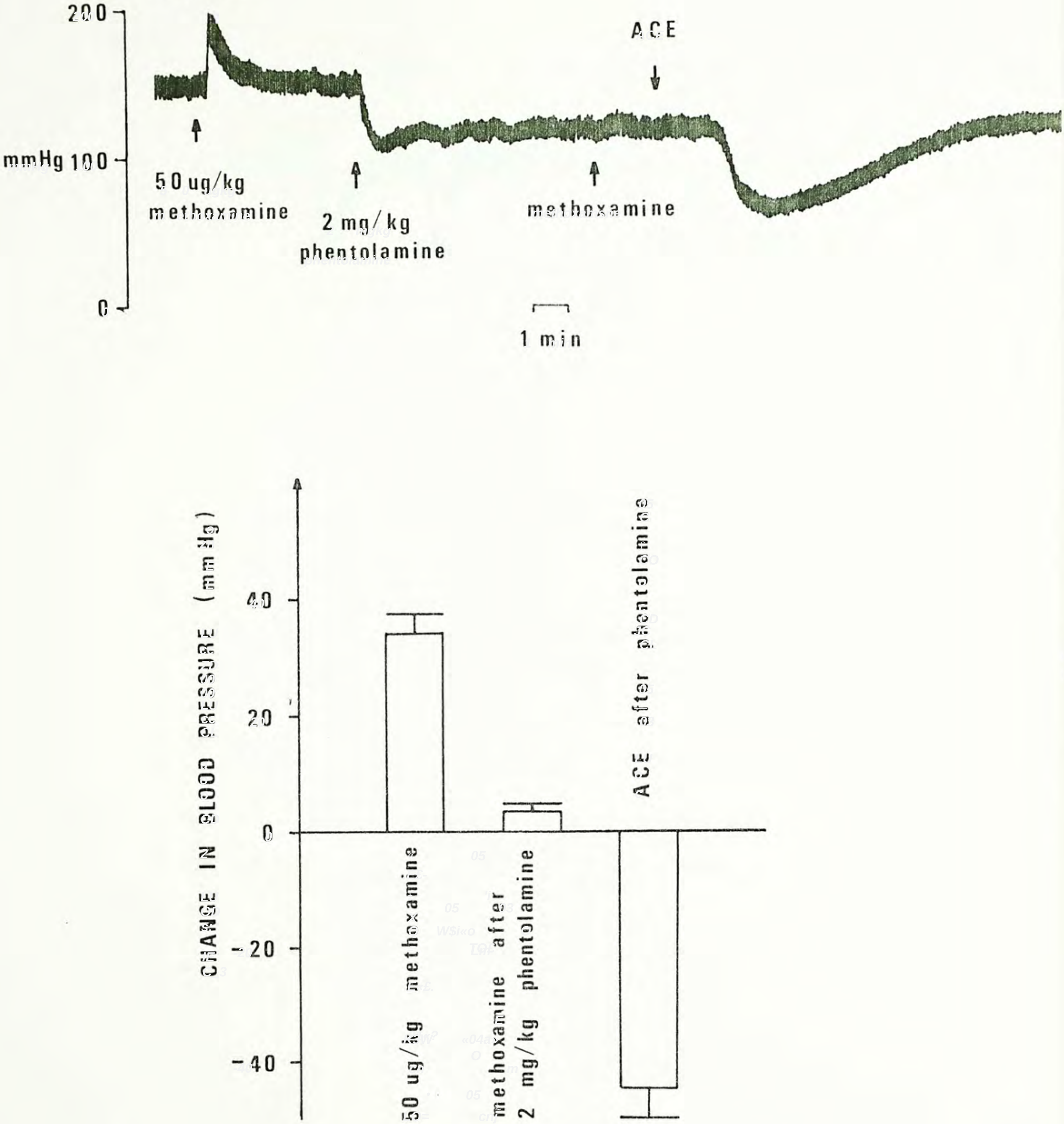

200
mmHg 100
0
50 ug/kg methoxamine
2 mg/kg phentolamine
methoxamine
ACE
1 min
CHANGE IN BLOOD PRESSURE (mmHg)
40
20
0
-20
-40
50 ug/kg methoxamine
methoxamine after 2 mg/kg phentolamine
ACE after phentolamine

Fig. 3.2.4a,b

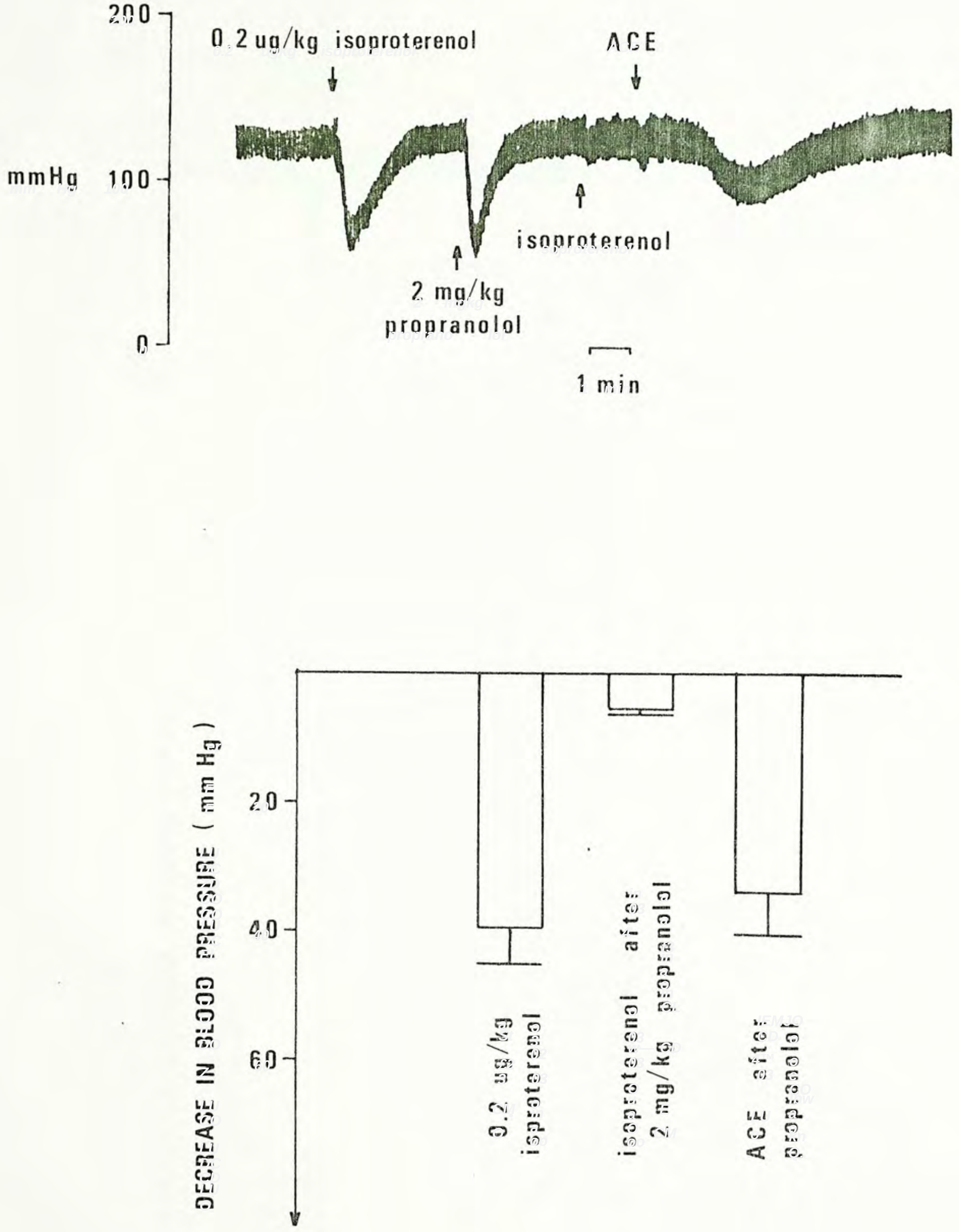

200
mmHg
100
0
0.2 ug/kg isoproterenol
ACE
isoproterenol
2 mg/kg propranolol
1 min
DECREASE IN BLOOD PRESSURE ( mm Hg )
20
40
60
0.2 ug/kg isproterenol
isoproterenol after 2 mg/kg propranolol
ACE after propranolol

Fig. 3.2.5a,b

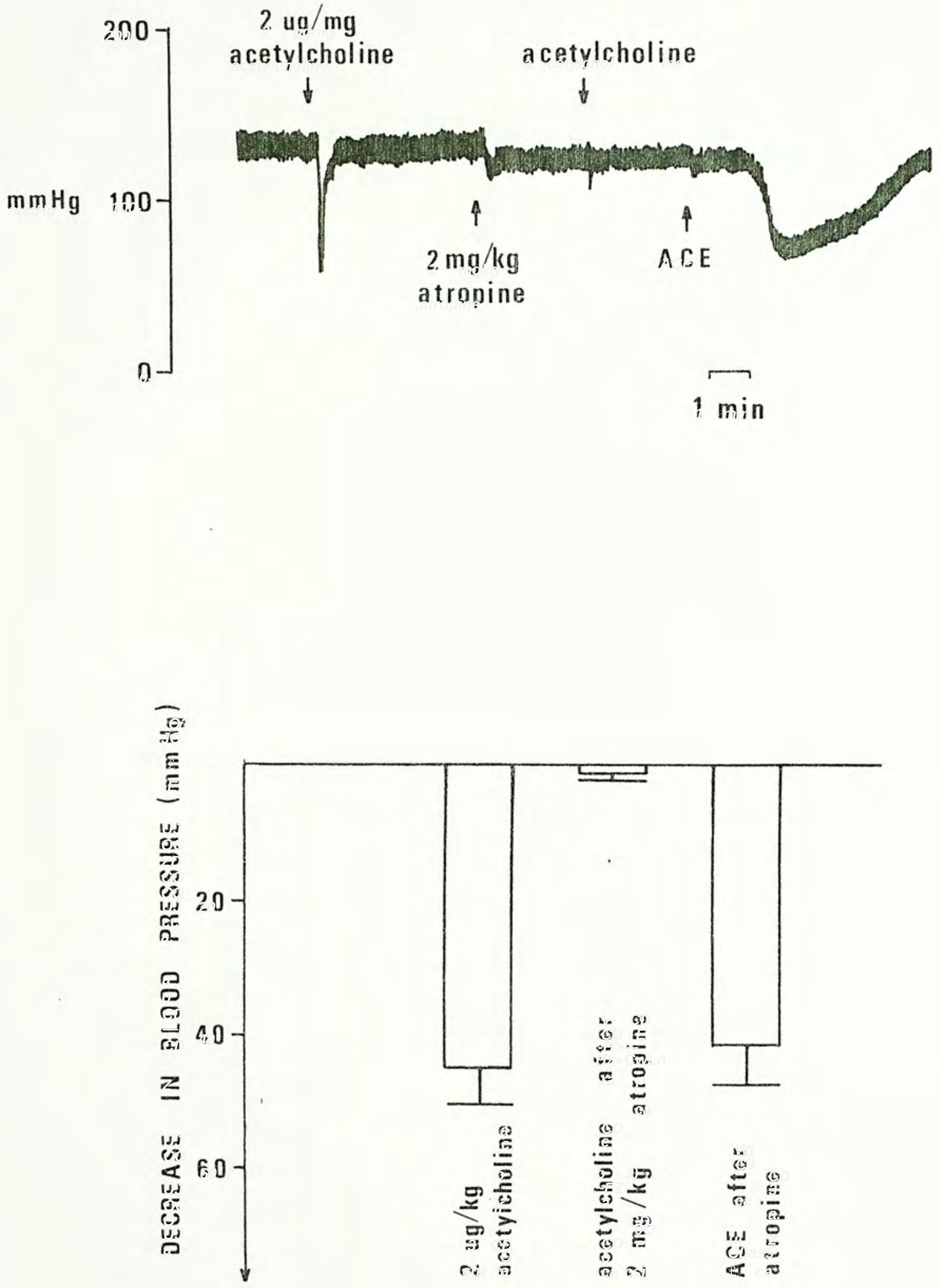

200
2 ug/mg
acetylcholine
acetylcholine
mmHg
100
2 mg/kg
atropine
ACE
0
1 min
DECREASE IN BLOOD PRESSURE (mm Hg)
20
40
60
2 ug/kg
acetylcholine
acetylcholine after
2 mg/kg atropine
ACE after
atropine

Fig. 3.2.6a,b

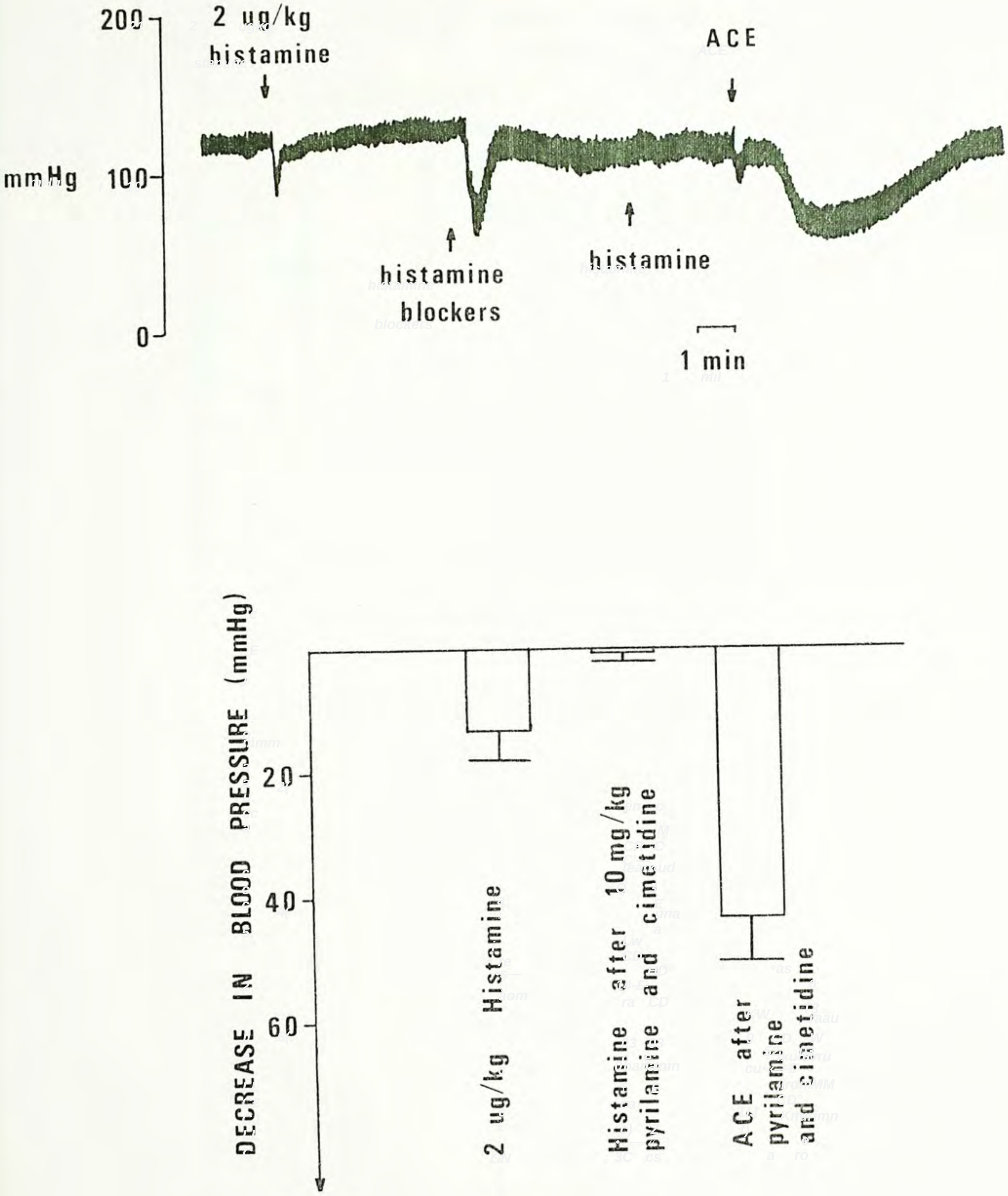

200
2 ug/kg
histamine
ACE
mmHg
100
histamine
blockers
histamine
0
1 min
DECREASE IN BLOOD PRESSURE (mmHg)
20
40
60
2 ug/kg Histamine
Histamine after 10 mg/kg
pyrilamine and cimetidine
ACE after
pyrilamine
and cimetidine

Fig. 3.2.71,b

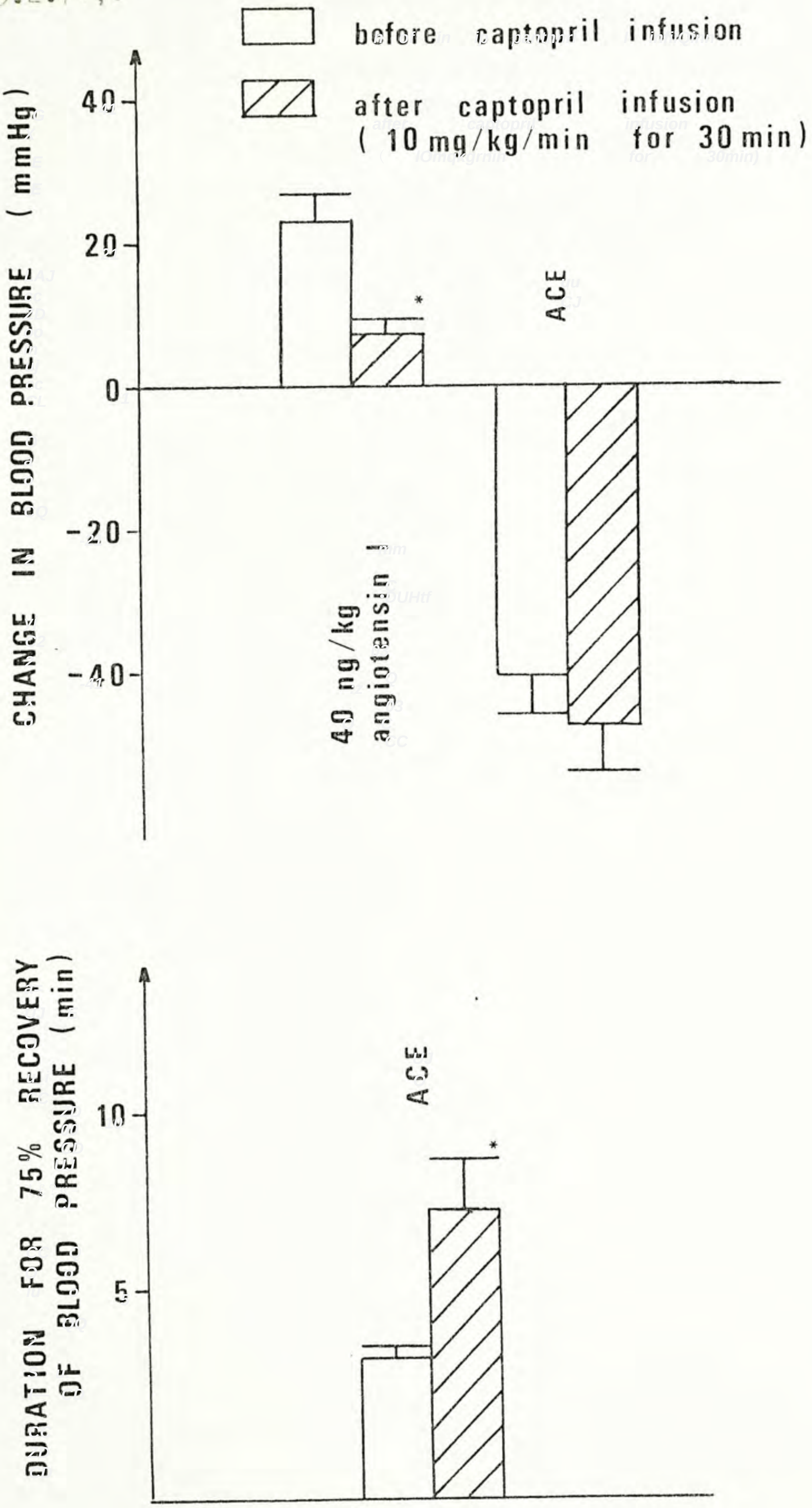

before captopril infusion
after captopril infusion
( 10 mg/kg/min for 30 min )
CHANGE IN BLOOD PRESSURE ( mmHg )
40
20
0
-20
-40
*
ACE
40 ng/kg angiotensin I
DURATION FOR 75% RECOVERY OF BLOOD PRESSURE (min)
10
5
ACE
*

Fig. 3.2.8a,b

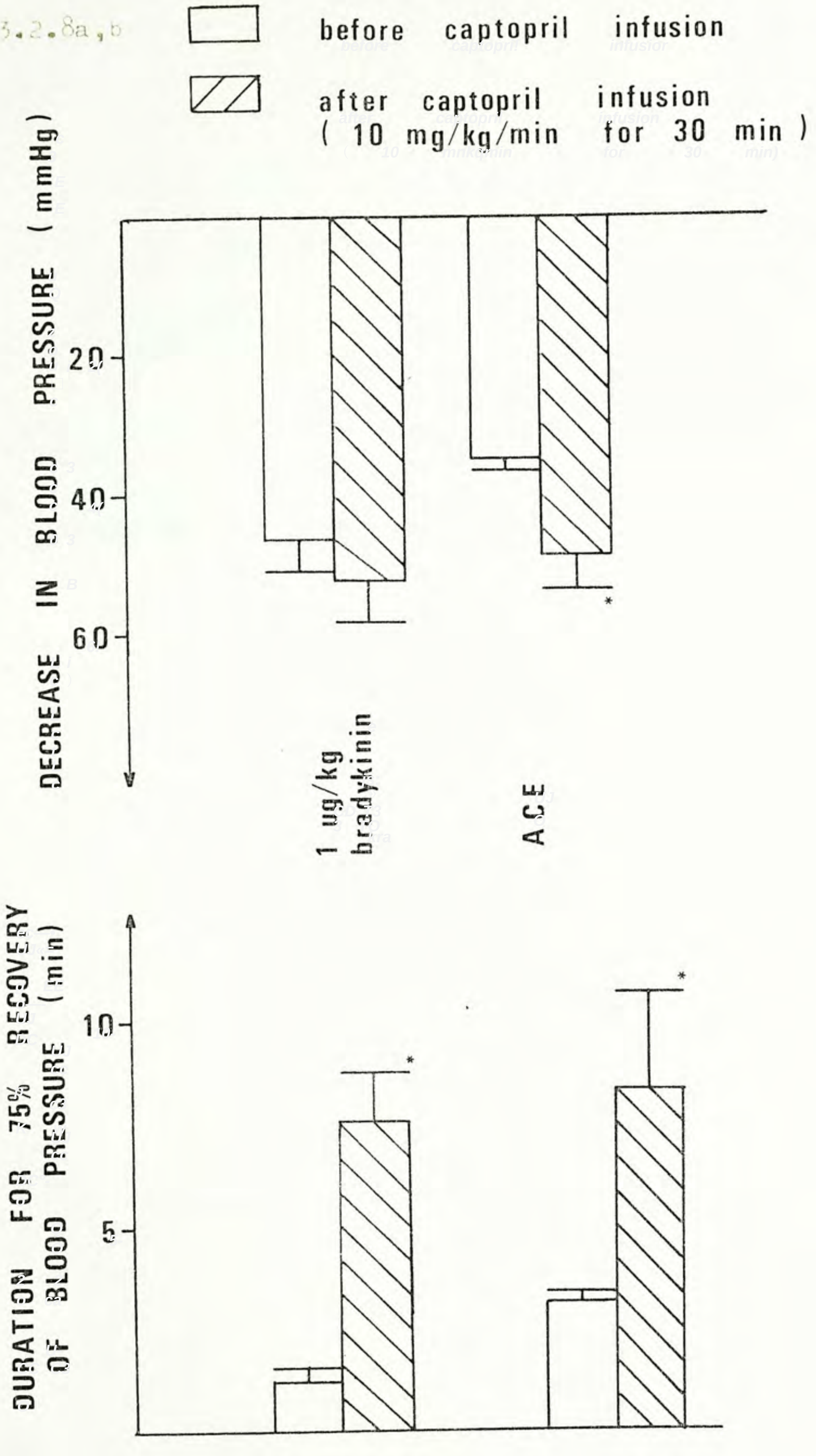

before captopril infusion
after captopril infusion ( 10 mg/kg/min for 30 min )
DECREASE IN BLOOD PRESSURE ( mmHg)
20
40
60
*
1 ug/kg bradykinin
ACE
DURATION FOR 75% RECOVERY OF BLOOD PRESSURE (min)
10
5
*
*

Fig. 3.2.9a,b

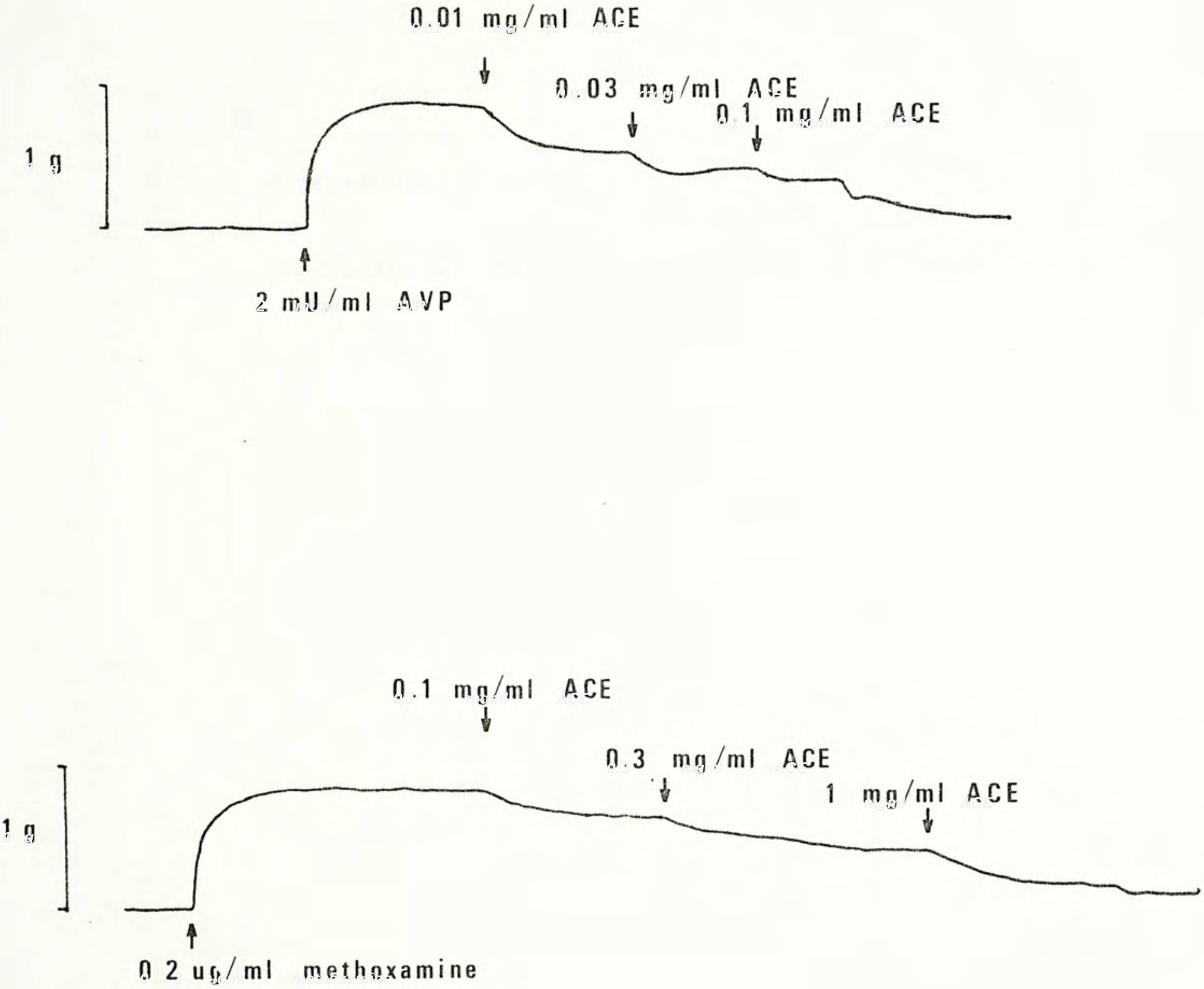
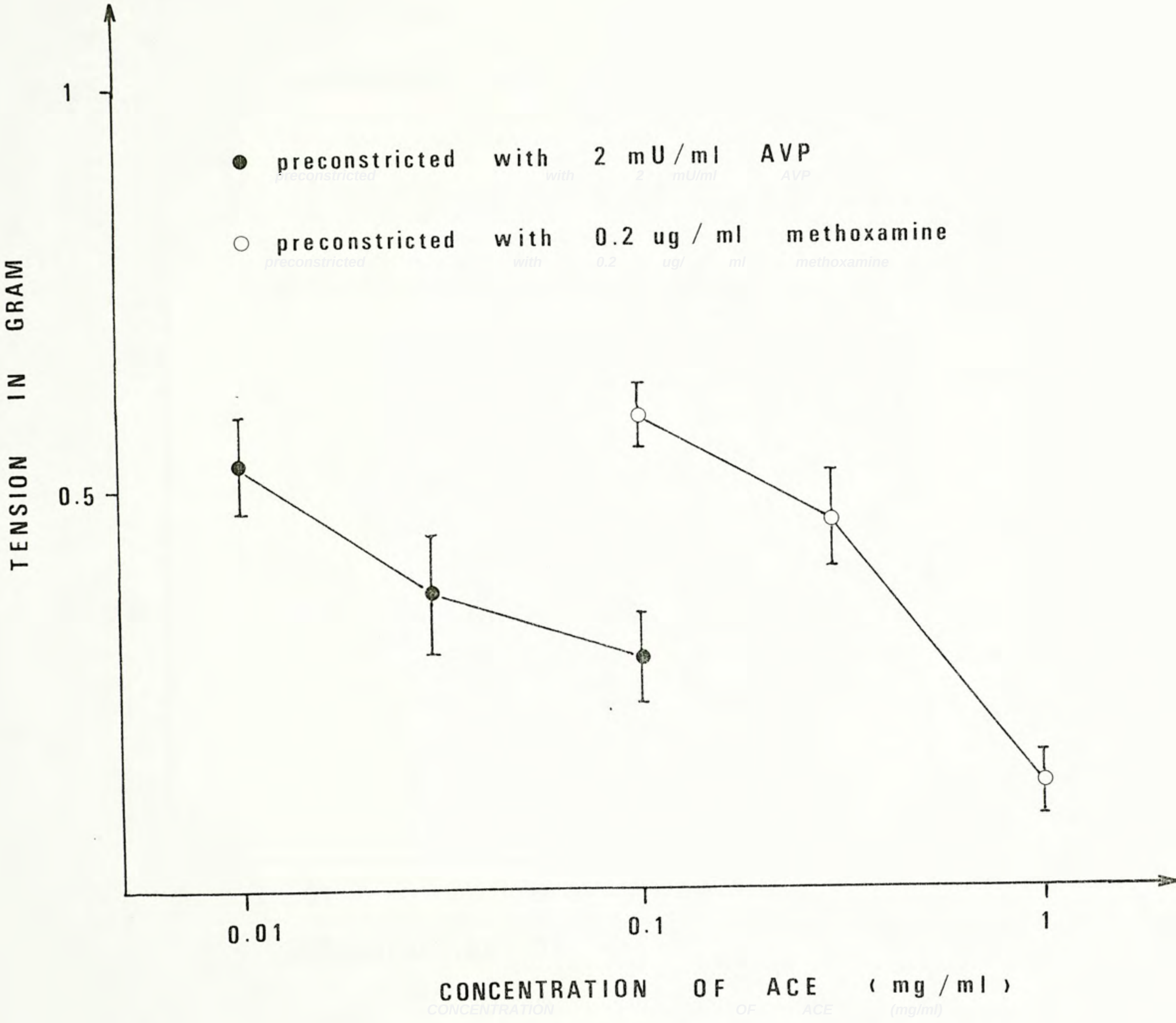
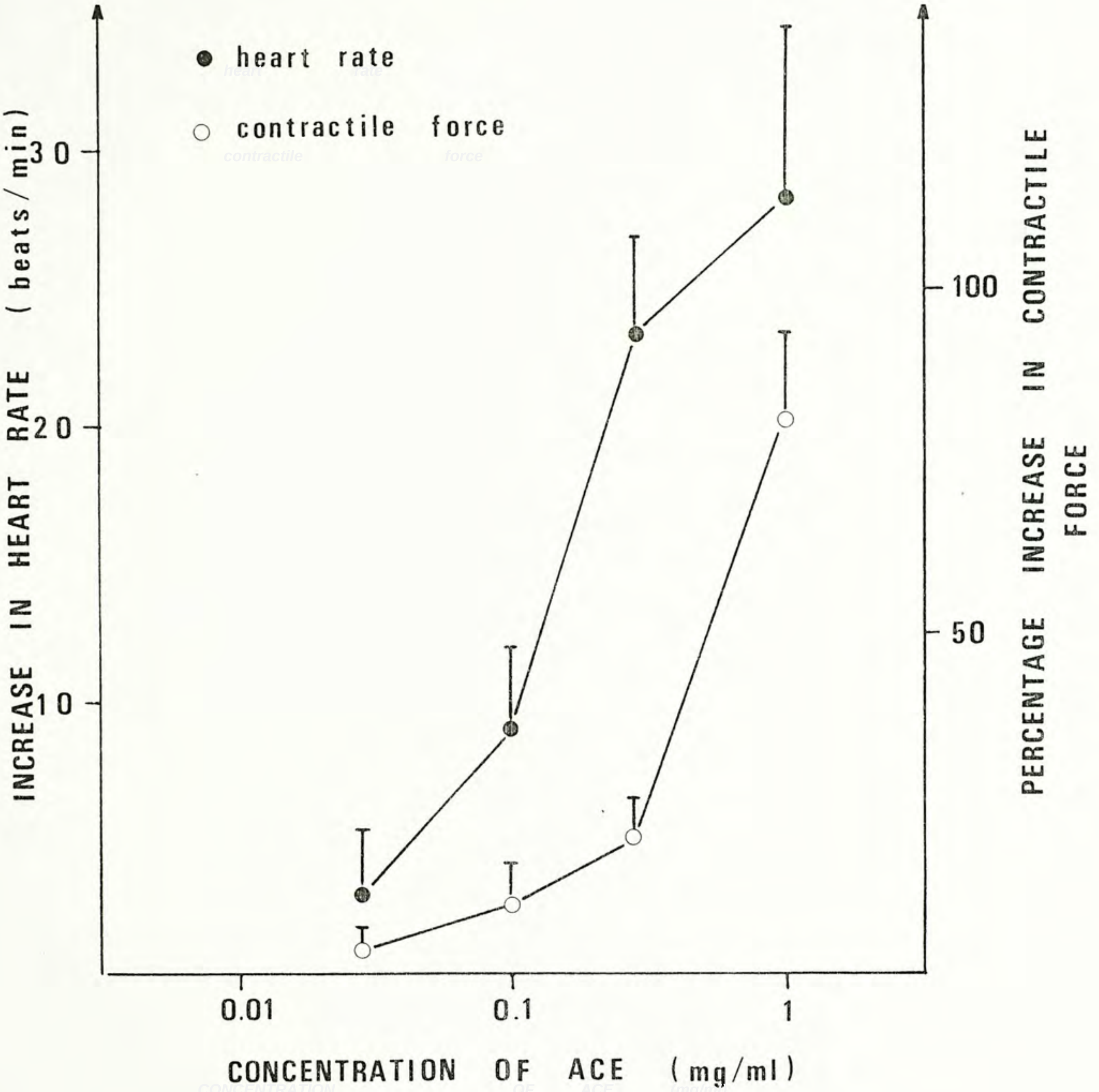

0.01 mg/ml ACE
0.03 mg/ml ACE
0.1 mg/ml ACE
1 g
2 mU/ml AVP
0.1 mg/ml ACE
0.3 mg/ml ACE
1 mg/ml ACE
1 g
0.2 ug/ml methoxamine

Fig. 3.2.10



TENSION IN GRAM
1
0.5
● preconstricted with 2 mU/ml AVP
○ preconstricted with 0.2 ug / ml methoxamine
0.01
0.1
1
CONCENTRATION OF ACE ( mg / ml )

Fig. 3.2.11


● heart rate
○ contractile force
INCREASE IN HEART RATE ( beats / min)
30
20
10
PERCENTAGE INCREASE IN CONTRACTILE FORCE
100
50
0.01
0.1
1
CONCENTRATION OF ACE (mg/ml)

# SECTION THREE

# PRELIMINARY STUDY ON THE CHEMICAL NATURE OF THE HYPOTENSIVE SUBSTANCES IN *CLEMATIS CHINENSIS*

The root of Clematis chinensis was chosen as the plant material for the present investigation. During the earlier study (section 1), the Clematis extract showed a very long lasting hypotensive effect, it, however, required a very high dosage to give the response ($ED_{50}$=90.67 mg/kg). Attempts were made to purify the plant material.

## MATERIALS AND METHODS

The dry plant material was extracted with various solvents : ethanol, methanol, acetone and/or hexane. After each extraction, the solvent was dried with vacuum rotary evaporator. The hypotensive activity of the extract was assay with two anesthetized rats in each step to assess the presence of hypotensive activity. The rats were prepared as before and the dosage used for the assay was 40 mg/kg. The schemes for the purification were detailed in Fig. 3.31, 3.32 and 3.33.

Fig. 3.3.1 Preliminary purification of *Clematis chinensis* (Scheme 1).

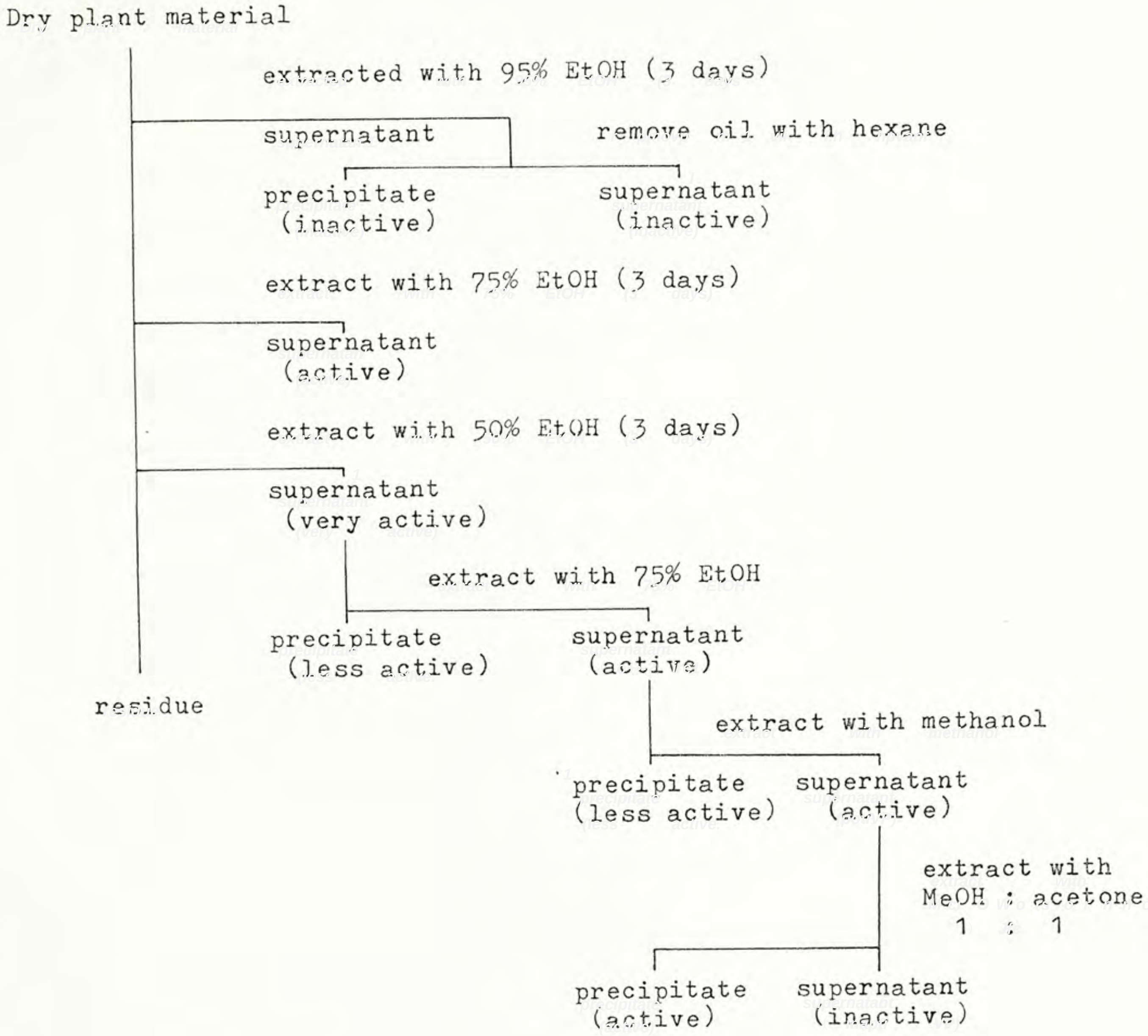


Fig. 3.3.2 Purification of Clematis chinensis (Scheme 2)

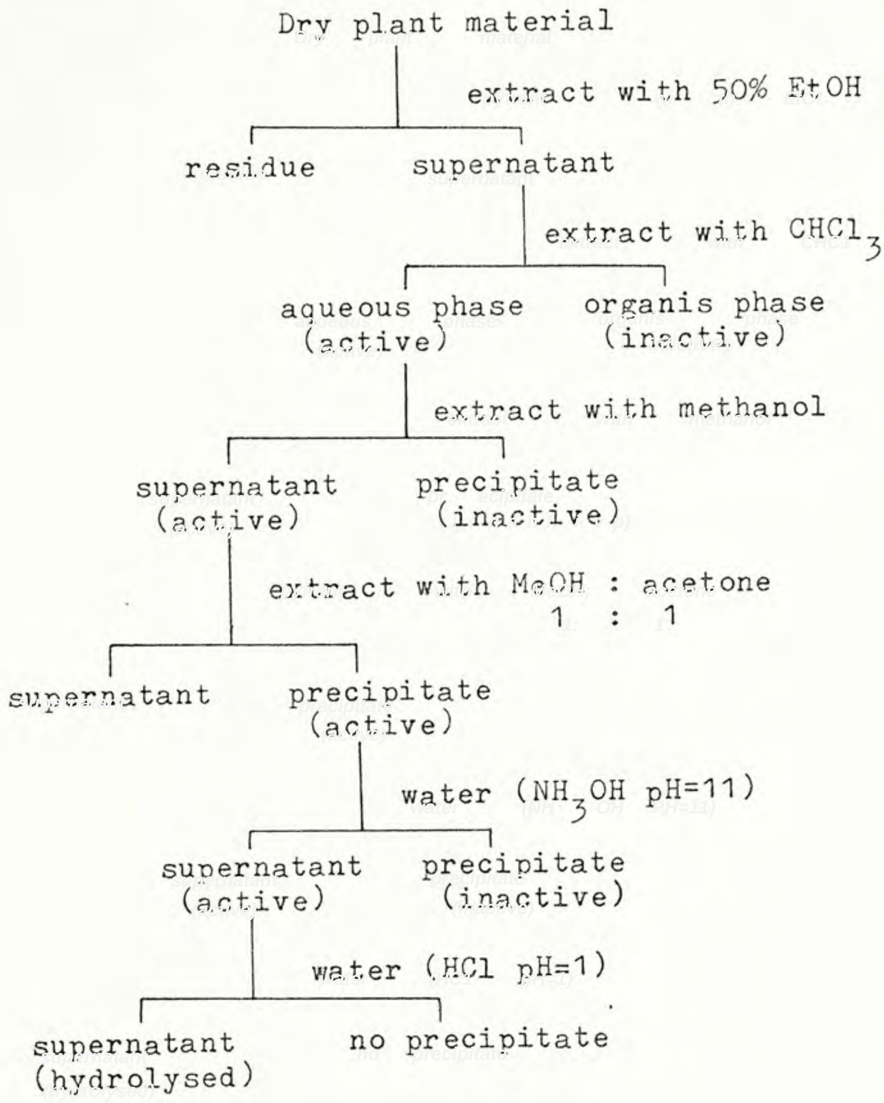
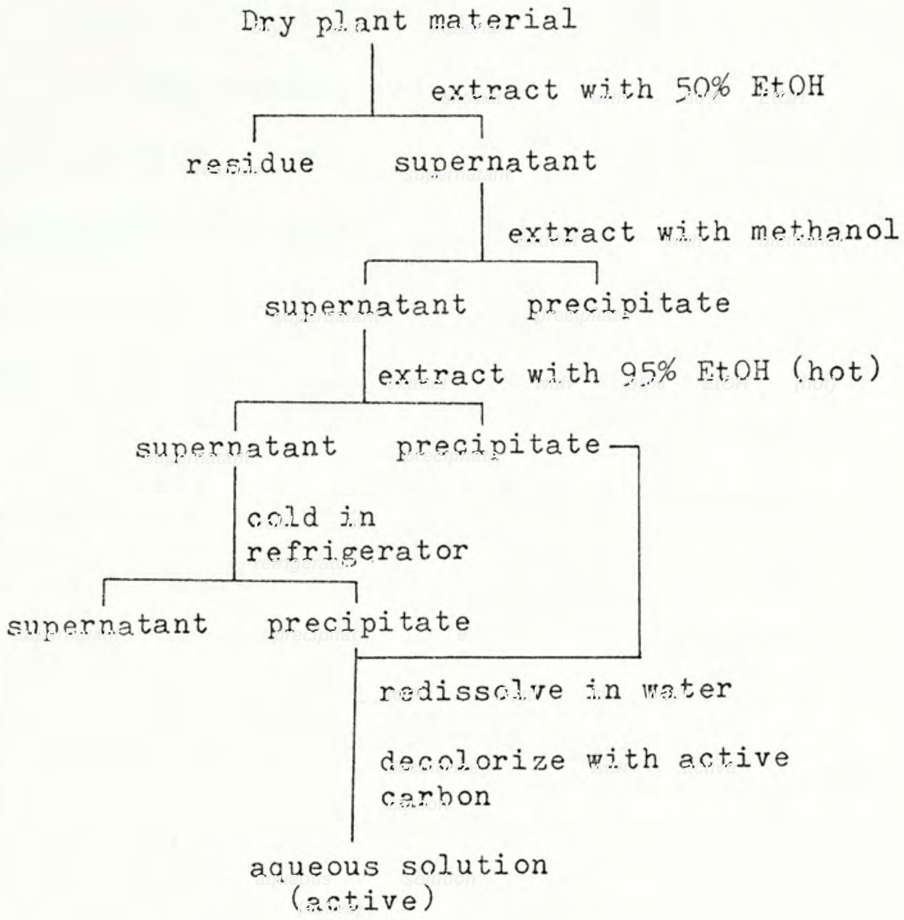


Fig. 3.3.3 Purification of *Clematis chinensis* (Scheme 3).



## RESULTS AND DISCUSIONS

In scheme 1, the purifying procedures focused on the polarity of the active hypotensive principles. It was found that they were readily extracted from the dry plant material by 50% EtOH. Further extractions showed that the active hypotensive principles is soluble in methanol but not in the mixture of methanol and acetone (1 : 1). Thus, it is quite polar in nature.

In scheme 2, strong acid and alkaline were used to determine the acid/base nature of the active principles. It was found to be acid in nature, since strong base could not precipite it out. However, when strong acid was tried, hydrolysis occurred. So it is unfeasible to use strong acid to purify the extract.

In scheme 3, active carbon was used to decolorize the semipurified extract. The hypotensive effect persisted after decolorization.

The relative hypotensive activity was indicated in parenthesis. Since only the relative activity was concerned, no absolute value of the depressor response was given. However, the purified material can produce a depressor response at dose of 40 mg/kg, comparable to that of the Clematis water extract at their maximum dosage (500 mg/kg) - a 50% decrease in MAP and the response lasted for more than half an hour.

Some chemical compounds have been isolated from Clematis. They include protoanemonin, anemonin, saponins and triterpenic olgosides (clematoside A,A',B,C) (92,93). Protoanemonin, anemonin and saponins are quite non-polar in nature. Based on the present data, they are not likely to be the active principles. Since the Clematis extract was susceptible to acid hydrolysis, it is speculated that some glycosides, probably clematosides, present in the extract may be responsible for the hypotensive action.

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# GLOSSARY

| | |
|---|---|
| *Abies sutchuerensis* | 朴松實 |
| *Acacia catechu* | 孩子茶 |
| *Achillea millefolium* | 洋蓍草 |
| *Achyranthes aspera* | 倒扣草 |
| *Achyranthes bidentata* | 牛膝 |
| *Aconitum carmichaeli* | 草烏頭 |
| *Acorus calamus* | 白菖[illegible] |
| *Ajuga lupulina* | 忽布筋骨草 |
| *Alisma plantago* | 泽瀉 |
| *Allium sativum* | 大蒜 |
| *Alstonia yunnanensis* | 紅辣樹根 |
| *Anacardium occidentale* | 都咸子 |
| *Anaphalis nepalensis* | 打火草 |
| *Andrographis paniculata* | 穿心蓮 |
| *Anethum graveoleus* | 蒔蘿茴 |
| *Angelica sinensis* | 當歸 |
| *Anisomeles indica* | 防風草 |
| *Apium graveolens* | 旱芹 |
| *Apocynum venetum* | 羅布麻 |
| *Arachis hypogaea* | 落花生枝葉 |
| *Aralia elata* | 刺老鴉 |
| *Ardisia japonica* | 紫金牛 |
| *Aristolochia contorta* | 馬兜鈴 |
| *Artemisia capillaris* | 茵陳蒿 |
| *Arundo donax* | 蘆竹根 |
| *Asarum heterotropoides* | 細辛 |
| *Asparagus officinalis* | 小百部 |
| *Astragalus membranaceus* | 黃耆 |
| *Berberis amurensis* | 小檗 |
| *Berberis heteropoda* | 黑果小檗 |
| *Berberis sargentiana* | 三顆針 |
| *Bidens tripartita* | 狼把草 |
| *Biota orientalis* | 側柏葉 |
| *Blumea balsamifera* | 艾納香 |
| *Blumea densiflora* | 大黑蒿 |
| *Caesalpinia crista* | 刺果蘇木 |
| *Calendula arvensis* | 金盞草 |
| *Calendula officinalis* | 金盞菊 |
| *Cannabis sativa* | 火麻仁 |
| *Capesium abrotanoides* | 火名精 |
| *Capsella bursa* | 薺菜 |
| *Caragana sinica* | 金雀根 |
| *Caediospermum halicacabum* | 假苦瓜 |
| *Carduus crispus* | 飛廉 |
| *Carthamus tinctorius* | 紅花 |
| *Cassia occidentalis* | 望江南子 |
| *Cassia tora* | 決明子 |
| *Catharanthus roseus* | 長春花 |
| *Celastrus orbiculatus* | 南蛇藤 |
| *Celosia argentea* | 青葙子 |

| | |
|---|---|
| Cephalanoplos segetum | 小薊 |
| Cerastium viscosum | 婆婆指甲菜 |
| Chelidonium majus | 白屈菜 |
| Chonemorpha megacalyx | 大萼鹿角藤 |
| Chrysanthemum indicum | 野菊花 |
| Cimicifuga acerina | 三面刀 |
| Cimicifuga foetida | 升麻 |
| Cimicifuga simplex | 野升麻 |
| Cinnamonum cassia | 肉桂 |
| Cirsium japonicum | 大薊 |
| Cistanche salsa | 肉蓯蓉 |
| Citrullus vulgaris | 西瓜子仁 |
| Citrus tangerina | 橘皮 |
| Cladonis alpestris | 太白花 |
| Cleiodendron trichotomum | 臭梧桐根 |
| Clematis chinensis | 威靈仙 |
| Clerodendron bungei | 臭牡丹根 |
| Clerodendron fragrans | 臭茉莉 |
| Clerodendron trichotomium | 臭梧桐 |
| Clerodendron yunnanense | 滇常山 |
| Cocculus laurifolius | 衡州烏药 |
| Codonopsis lanceolata | 山海螺 |
| Codonopsis pilosula | 黨參 |
| Commelina communis | 野跖草 |
| Convolvulus arvensis | 田旋花 |
| Coptis chinensis | 黃連 |
| Corydalis decumbens | 夏天無 |
| Crataegus pinnatifida | 山楂 |
| Curculigo orchioides | 仙茅 |
| Curcuma longa | 姜黃 |
| Cynanchum paniculatum | 徐長卿 |
| Cynoglossum officinale | 药用倒提壺 |
| Cyrtomium fortunei | 昝雞頭 |
| Dactylicapnos scandens | 紫金龍 |
| Diospyros kaki | 柿漆 |
| Dracocephalum heterophyllum | 白花夏枯草 |
| Dryopteris laeta | 花葉狗牙七 |
| Epimedium grandiflorum | 淫羊藿 |
| Equisetum arvense | 問荊 |
| Ervatamia hainaensis | 單根木 |
| Erysimum cheiranthoides | 桂竹糖芥 |
| Eucommia ulmoides | 杜仲 |
| Eupatorium lindleyanum | 野馬追 |
| Evodia rutaecarpa | 吳茱萸 |
| Fagopyrum esculentum | 蕎麦秸 |
| Ficus carica | 無花果 |
| Fritillaria cirrhosa | 川貝母 |
| Galium aparine | 八仙草 |
| Gardenia jasminoides | 梔子 |
| Gentiana macrophylla | 秦艽 |
| Gentiana scabra | 龍胆 |

| | |
|---|---|
| Glechoma longituba | 金錢草 |
| Gnaphalium hypoleueum | 天水蟻草 |
| Gnaphalium uliginosum | 濕鼠曲草 |
| Helictenes angustifolia | 山芝麻 |
| Helianthus annuus | 向日葵葉 |
| Heliotropium indicum | 大尾搖 |
| Hibiscus rosa | 扶桑花 |
| Holarrhena antidysenterica | 止瀉木皮 |
| Ilex pubescens | 毛冬青 |
| Imperata cylindrica | 白茅根 |
| Ipomoea digitata | 藤商陸 |
| Ixeris chinensis | 山苦賣 |
| Ixora chinensis | 龍船花 |
| Juglans regia | 胡桃葉 |
| Laminaria japonica | 昆布 |
| Lantana camara | 五色梅 |
| Lobelia chinensis | 半邊蓮 |
| Leontice robustum | 紅毛七 |
| Leonurus heterophyllus | 益母草 |
| Lingustrum japonicum | 苦茶葉 |
| Ligusticum wallichii | 山芎 |
| Linaria vulgaris | 柳穿魚 |
| Lithocarpus polystachyus | 多穗石柯葉 |
| Luffa cylindrica | 絲瓜葉 |
| Luisia morsei | 釵子股 |
| Lycoris radiata | 石蒜 |
| Lycum chinense | 地骨皮 |
| Lysimachia barystachys | 狼尾巴花 |
| Lysimachia insignis | 三張葉 |
| Lysimachia hattiana | 黃開口 |
| Lysimachia vulgaris | 黃蓮花 |
| Maesa indica | 兩面青 |
| Magnolia liliflora | 木蘭皮 |
| Mahonia bealei | 十大功勞葉 |
| Malachium aquaticum | 鵝腸草 |
| Malus pumila | 萍果 |
| Menispermum dauricum | 蝙蝠葛 |
| Menyanthes trifoliata | 睡菜根 |
| Mesona chinensis | 涼粉草 |
| Morus alba | 桑根 |
| Musa basjoo | 芭蕉根 |
| Nelumbo nucifera | 蓮子心 |
| Nitraria sibirica | 卡密 |
| Nymphaea tetragona | 睡蓮 |
| Oenanthe benghalensis | 水芹菜 |
| Oenanthe javanica | 水芹 |
| Paeonia lactiflora | 赤芍藥 |
| Paederia scandens | 雞屎藤 |
| Paeonia suffruticosa | 牡丹皮 |
| Panax ginseng | 人参 |

| | |
|---|---|
| Panax pseudo-ginseng | 三七 |
| Panicum repens | 鋪地黍根 |
| Peganum harmala | 駱駝蓬子 |
| Phellodendron amurense | 黄柏 |
| Phyllanthus emblica | 油柑根 |
| Piper longum | 荜茇根 |
| Piptanthus concolor | 黄花木 |
| Pittosporum glabratum | 山枝根 |
| Plantago asiatica | 車前 |
| Plumbago indica | 紫雪花 |
| Polygonum aviculare | 萹蓄 |
| Polygonum chinense | 火炭母草 |
| Polygonum hydropiper | 水蓼 |
| Polygonatum sibiricum | 黄精 |
| Polygonatum verticillatum | 羊角参 |
| Prunella vulgaris | 夏枯草 |
| Prunus persica | 桃仁 |
| Pueraria lobata | 葛根 |
| Pyrus pashia | 山里紅 |
| Pyrola rotundifolia | 鹿銜草 |
| Ranunculus chinensis | 回回蒜 |
| Rauwolfia verticillata | 萝芙木 |
| Rehmannia glutinosa | 干地黄 |
| Rhaponticum uniflorum | 漏芦 |
| Rhododendron micranthum | 照山白 |
| Rhododendron molle | 六軸子 |
| Rosmarinus officinalis | 迷迭香 |
| Salix babylonica | 柳葉 |
| Salsola collina | 猪毛菜 |
| Salsola ruthenica | 刺蓬 |
| Salvia mittiorrhiza | 丹参 |
| Sapindus mukorossi | 無患子皮 |
| Sargassium fusiforme | 海藻 |
| Sausaurea lappa | 木香 |
| Scopolia acutangula | 三分三 |
| Scrophularia ningpoensis | 玄参 |
| Scutellaria baicalensis | 黄芩 |
| Sedum kamtschaticum | 费菜 |
| Sedum multicaule | 佛指甲 |
| Siegesbeckia orientalis | 豨莶 |
| Sinomenium acutum | 青風藤 |
| Solanum nigrum | 古鈕菜 |
| Sophora japonica | 槐花 |
| Stephania cepharantha | 白药子 |
| Stephania japonica | 千金藤 |
| Stellaria saxatilis | 地精草 |
| Stephania tetrandra | 防己 |
| Sterculia scaphigera | 胖大海 |
| Stereocaulon paschale | 石寄生 |
| Swertia heterantha | 鳥金草 |
| Symplocos caudata | 山矾葉 |

| | |
|---|---|
| *Syzygium aromaticum* | 丁香 |
| *Tacca plantaginea* | 水田七 |
| *Tecomaria capensis* | 竹林标 |
| *Thalictrum foliolosum* | 馬尾蓮 |
| *Thermopsis alpina* | 高山黄华根 |
| *Trachycarpus wagnerianus* | 棕櫚花 |
| *Tribulus terrestris* | 刺蒺藜 |
| *Trillium tschonoskio* | 竿儿七 |
| *Typha angustala* | 蒲黄 |
| *Uncaria macrophylla* | 大葉鈎藤 |
| *Uncaria rhynchophylla* | 鈎藤 |
| *Urtica cannabina* | 蕁麻根 |
| *Usnea longissima* | 松蘿 |
| *Valeriana officinalis* | 纈草 |
| *Veratrum nigrum* | 藜芦 |
| *Verbascum thapsus* | 毛蕊花 |
| *Veronica anagallis-aquatica* | 水苦蕒 |
| *Vicia faba* | 蚕豆花 |
| *Vinca minor* | 藤長春 |
| *Viscum angulatum* | 棱枝槲寄生 |
| *Viscum articulatum* | 楓香寄生 |
| *Viscum coloratum* | 槲寄生 |
| *Wedelia prostrata* | 卤地菊 |
| *Xanthium sibiricum* | 蒼耳根 |
| *Zanthoxylum bungeanum* | 花椒 |
| *Zea mays* | 玉米鬚 |
| *Ziziphus jujuba* | 酸枣根皮 |

# CORRIGENDUM

| Page no. | Line no. | In text | should read |
|---|---|---|---|
| content | 7 | Medicinal | Medicine |
| 2 | 2 | vaspressin | vasopressin |
| 3a | 11 | plant | plants |
| 5 | 11 |  | generations orally and |
| 5 | 20 | studied | studies |
| 6 | 10 | areca | Areca |
| 6 | 21 | Digitalis purpurea | Digitalis purpurea |
| 7 | 3 | informations | information |
| 7 | 7 |  | now be shown |
| 10 | 5 | focus | foci |
| 10 | 16 | informations | information |
| 11 | 1 | womwn's | women's |
| 11 | 3 | gynecology | gynaecology |
| 11 | 16 | knoen | known |
| 11 | 20 | family | families |
| 11 | 24 | taxononmy | taxonomy |
| 11 | 24 | Howver | However |
| 12 | last | combination | combinations |
| 13 | 7 | invigorate | invigorating |
| 13 | 7 | promote | promoting |
| 13 | 12 | ternata | ternata |
| 13 | 19 | Ther | There |
| 14 | 4 | componds | compounds |
| 15 | 2 | ahows | shows |
| 15 | 7 | neglect | neglects |
| 15 | 19 | stoping | stopping |
| 15 | 21 | bowls | bowels |
| 15 | 22 | bland flavored | bland-flavored |
| 16 | 13 | detoxication | detoxification |
| 17 | 10 | chinese | Chinese |
| 40 | 3 | distinquish | distinguish |
| 40 | 4 | with | from |
| 40 | 7 | goal | goals |
| 40 | 13 | contains | contain |
| 41 | 22 | adenin | adenine |
| 41 | 24 | floribunda | floribunda |
| 42 | 10 |  | reported to contain |
| 42 | 15 | has | have |
| 43 | 14 |  | was isolated |
| 43 | 15 | for | to |
| 43 | 21 | are | is |
| 44 | 9 | flavanoid | flavonoid |
| 45 | 7 | hypotension | hypotensive |
| 45 | 8 | flavanoid | flavonoid |
| 45 | 19 | is | are |
| 62 | 10 | electric | electrical |
| 62 | 13 | neurone | neurons |
| 62 | 14 | adreoceptors | adrenoceptors |
| 66 | 19 | injection | injections |

| | | | |
|---|---|---|---|
| 68 | 9 | outlines | outlined |
| 70 | 2nd last | P 0.05 | $P<0.05$ |
| 72 | 5 | temporary | temporarily |
| 73 | 5 | adjuded | adjudged |
| 75 | 6 | vasodilatlation | vasodilatation |
| 75 | 13 | occur | occurs |
| 75 | 19 | amount | among |
| 77 | 3 | dosage | dosages |
| 77 | last | dosage | dosages |
| 90 | 2 | choosen | chosen |
| 96 | 4 | cummulative | cumulative |
| 97 | 7 | t-test | t-tests |
| 98 | 8 | | [Mean (95% confidence interval |
| 98 | 12 | 39.3 | 39.3±1.2 |
| 100 | 2nd last | antagonist | antagonists |
| 103 | 5 | | are about the same |
| 103 | 16 | immulogical | immunological |
| 104 | 11 | extend | extent |
| 104 | 15 | arteriole | arterioles |
| 105 | 2nd last | bradykininwere | bradykinin were |
| 106 | 4 | do | does |
| 106 | 6 | sngiotensin | angiotensin |
| 106 | 9 | does | is |
| 106 | 9 | | likely to produce |
| 106 | 11,13,14 | | α-adrenergic |
| 106 | 16 | suggest | suggests |
| 106 | 22 | negative | negatively |
| 107 | 15 | vasoconstrition | vasoconstriction |
| 108 | 8 | componds | compounds |
| 126 | 5 | assay | assayed |
| 128 | 6 | organis | organic |
| 128 | 14 | $NH_3OH$ | $NH_4OH$ |
| 129 | 9 | cold | cool |
| 130 | 1 | DISCUSIONS | DISCUSSION |
| 130 | 12 | precipite | precipitate |
| 131 | 1 | | at a dose |
| 131 | 7 | olgosides | oligosides |
| 134 | 11 | evolution | Evolution |
| 135 | 19 | on | of |
| 140 | 16 | | α-receptors |
| 142 | 12 | Cardoxyalkanoyl | carboxyalkanoyl |
| 142 | 2nd last | norepinepinephrine | norepinephrine |
| 142 | last | tissue | tissues |
| 144 | 21 | Hambrg | Hamberg |